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Neurocognitive Characterizations of Russian Heroin Addicts without a Significant History of Other Drug Use

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Abstract

Research on the neurocognitive characteristics of heroin addiction is sparse and studies that do exist include polydrug abusers; thus, they are unable to distinguish neurocognitive effects of heroin from those of other drugs. To identify neurocognitive correlates specific to heroin addiction, the present study was conducted in St. Petersburg, Russia where individuals typically abuse and/or become addicted to only one substance, generally alcohol or heroin. Heroin addicts were recruited from an inpatient treatment facility in St. Petersburg. Three comparison groups included alcoholics, addicts who used both alcohol and heroin, and non-abusers. Psychiatric, background, and drug history evaluations were administered after detoxification to screen for exclusion criteria and characterize the sample. Executive Cognitive Functions (ECF) that largely activate areas of the prefrontal cortex and its circuitry measured include complex visual pattern recognition (Paired Associates Learning), working memory (Delayed Matching to Sample), problem solving (Stockings of Cambridge), executive decision making (Cambridge Decision Making Task), cognitive flexibility (Stroop Color-Word Task) and response shifting (Stop Change Task). In many respects, the heroin addicts were similar to alcohol and alcohol\heroin dependent groups in neurocognitive deficits relative to controls. The primary finding was that heroin addicts exhibited significantly more disadvantageous decision making and longer deliberation times while making risky decisions than the other groups. Because the nature and degree of recovery from drug abuse are likely a function of the type or pattern of neurocognitive impairment, differential drug effects must be considered.

Keywords

heroin addiction; cognition; neuropsychology; alcoholism; Russia

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1. Introduction

Surprisingly little research exists on the neurocognitive characteristics of chronic heroin use. This situation persists despite the global existence of millions of heroin addicts, as well as young initiates, who have no knowledge of heroin's potential adverse effects on brain function. A majority of studies in the U.S. and elsewhere include polydrug abusers; thus, although there are indications of various neuropsychological deficits in this group, we are unable to precisely distinguish between neurocognitive correlates of heroin versus the influence of other drugs (Grant et al., 1978a, 1978b; Parsons and Farr, 1981). Even within groups with a known "drug of choice" or single drug dependence, in the overwhelming majority of cases there is a significant history of other drug and alcohol abuse. Extensive use of alcohol is particularly common among illicit drug abusers in the U.S. and, due to the well-documented insidious and global effects of alcohol on cognitive function (Harper and Matsumoto, 2005), it has been impossible to isolate the potential cognitive deficits associated with heroin.

Given evidence for the differential associations between chronic use of various drugs and neurocognitive functions (Bolla et al., 2000; Selby and Azrin, 1998), important research questions are: Are particular neurocognitive deficits associated specifically with heroin addiction or are they related to the potentially overshadowing effect of alcohol use, and is there an additive effect of both heroin and alcohol on cognitive function? Higher-order neuropsychological abilities, or executive cognitive functions (ECFs) modulated by the prefrontal cortex, were the focus of this investigation given evidence that the extent and nature of prefrontal neurotoxicity and its related functional deficits associated with heroin and alcohol may be distinguishable (Ersche et al., 2006; Hill et al., 1979; Mandal et al., 2000; Wolf et al., 1979). Hypotheses are based on knowledge of differential acute pharmacological effects of alcohol and heroin and the neuropsychological literature focusing on heroin addicts with a history of polydrug abuse as detailed in the following sections.

1.1 Neuropsychological Deficits in Heroin Addicts

Numerous studies have examined the functional correlates of heroin's potential neurotoxic actions in the form of neuropsychological performance. However, because heroin is a "late-stage" drug in most countries (i.e., most drug users "graduate" to heroin use only after extensive use of other drugs and alcohol [Zinkernagel et al., 2001]), no studies have isolated specific correlates of heroin addiction (Rogers and Robbins, 2001), with one exception. Fields and Fullerton (1975) studied Vietnam veterans who reported being dependent primarily upon heroin (averaging 4.9 yrs) with no history of excessive use of other drugs or alcohol. Using the Halstead Battery, the veterans performed as well as the control groups and unlike brain-damaged patients, with the exception of the abstract reasoning subtest on which heroin addicts performed less well than the controls. This study is relevant given that these subjects tended to be single drug users and were less likely to have an existing predisposition to drug abuse that might play a role in another environment or that may have predicted neurocognitive impairment (Robins et al., 1980). The latter scenario is often reported for those with a family history of alcoholism which significantly predicts cognitive dysfunction, as well as earlier age of drug use onset, for heroin addicts (Rodriguez, 1994).

Early studies were discrepant in their findings, with some reporting no remarkable differences in neuropsychological measures between heroin addicts and comparison groups, even in the context of long-term use of high doses of heroin (Brown and Partington, 1942; Strang and Gurling, 1989) while others found significant perceptual-motor, memory, attention and concentration, and intelligence deficits relative to controls (Ahmad et al., 1989; Wolf et al., 1979; Korin, 1974; Rounsaville et al., 1981). Due to the timing of these studies, however, more traditional and less sophisticated tests of neuropsychological function were used, comparison groups were not always appropriate for this population (e.g., brain damaged patients), and

concomitant use of other drugs and alcohol were not accounted for. More recent studies have utilized test batteries with greater sensitivity to dimensions of ECFs and greater specificity in terms of the neuroanatomical loci associated with these functions.

1.1.1 Studies with Normal Control Subjects—Abstinent heroin addicts and normal controls were examined by Pau et al. (2002) including measures of sustained attention, divided attention, impulse control, and cognitive flexibility and abstract reasoning. The only significant performance decrement exhibited by heroin addicts was on the measure of cognitive impulsivity. One neuroimaging (fMRI) study links performance on this task to activation of bilateral areas of the prefrontal cortex, subcortical and cortical motor areas (Kirsch et al., 2006). Two additional studies included tasks that largely recruit the orbitofrontal portion of the prefrontal cortex (OFC). Rogers et al. (1999a) used the Cambridge Decision-Making Task (CDMT) to measure risk taking relative to reward/penalty sensitivity (Rogers et al., 1999a), a dimension of affective impulsivity, to compare heroin addicts with normal controls (and also amphetamine abusers). Heroin addicts did not exhibit decision making deficits; however, they did deliberate longer. In contrast, however, Madden et al. (1997) used a delay discounting task to assess affective impulsivity in the context of delayed rewards and reported that, given choices between small immediate rewards and larger delayed rewards, heroin abusers tended to choose the smaller rewards more frequently than did normal controls and the effect was magnified when the reward was heroin rather than money.

1.1.2 Studies with an Amphetamine Abusing Comparison Group—Most studies including amphetamine abusers as comparisons found that amphetamine abusers exhibited more severe deficits; the nature and extent of the deficits were task specific. In the Rogers et al. study mentioned above (1999a), amphetamine users showed greater disadvantageous decision making (affective impulsivity) than the chronic opiate users and normal controls on the CDMT, however both drug groups exhibited significantly delayed deliberation times on risky trials relative to controls. Differential associations were also found by Ornstein et al. (2000) who reported reductions in cognitive flexibility in amphetamine users whereas the heroin abusers were impaired in learning an easier attentional set component thought to recruit bilateral inferior frontal sulci (Konishi et al., 1999). Also, heroin abusers failed to improve after training on a sequence generation task and showed more perseverative behavior on the task. Both groups were impaired on some tests of spatial working memory and pattern recognition memory, reflective of temporal lobe dysfunction.

1.1.3 Studies with a Methadone Maintained Comparison Group—A number of studies compared the cognitive function of heroin addicts with ex-addicts who are maintained on methadone (MMT)(Gritz et al., 1975;Verdejo et al., 2005). Of particular relevance to the present study, Ersche et al. (2005) administered the CDMT to assess affective impulsivity. Increased risk-taking behavior was notable in the MMT group but, unexpectedly, not in the opiate users despite their risky lifestyles. These studies suggest that methadone use is associated with greater OFC impairments relative to current heroin use alone. These differences may arise either from methadone's distinctive pharmacological actions and properties or from recency of drug use, although in Ersche et al., opiates were used during the study period. The latter scenario suggests that abstinence may promote some cognitive improvements, although this possibility remains untested.

1.1.4 Summary of Findings—Heroin addicts with polysubstance abuse histories tended to perform worse than controls but better than amphetamine users particularly on various dimensions of impulsivity, attention, learning, working memory and pattern recognition, all primarily prefrontal functions. The few discrepancies in the literature may be a function of task and population differences (e.g., Ornstein et al., 2000 versus Ersche et al., 2006). Only one

early study compared heroin addicts with a history of polydrug abuse to alcoholics (Wolf et al., 1979); alcoholics were twice as impaired as the heroin addicts, particularly in abstraction ability and reasoning. Taken together, these studies suggest that (i) the association between chronic drug use and varying patterns of cognitive deficits may be a function of the differential effects of specific drugs largely on prefrontal brain circuits or prefrontal deficits that predated and possibly predisposed to drug abuse, (ii) current use of opiates and MMT, in particular, may be responsible for many of the deficits often found in addicts, and (iii) abstinence may promote some cognitive improvements in certain drug groups but not others, with mixed results for heroin users (Ersche et al., 2006; Gritz et al., 1975; Papageorgiou et al., 2004; Verdejo et al., 2005).

1.2 Aims of the Current Study

In order to elucidate the neurocognitive characteristics of heroin addicts that may exist independently of alcohol and other drugs, it is necessary to examine a population with a history of single drug dependence. Thus, the present study was conducted in St. Petersburg, Russia where a unique pattern of drug use exists. Heroin addicts tend to have tried alcohol early in adolescence and then begin experimenting, rapidly developing a preference for heroin and discontinuing all other drug use (typically alcohol, marijuana and ephedrine). Another much larger group of Russians who become alcoholics tend to have initiated alcohol in their early teenage years and persist in using only alcohol throughout their addiction career. They do not use other drugs. A third group is comprised of heroin addicts who enter treatment and eventually abstain from heroin only to develop alcoholism. The inclusion of this group enables a determination of whether there is an additive “effect” on cognitive function when both heroin and alcohol are abused, as demonstrated in cocaine and cocaine+alcohol abusers (Bolla et al., 2000). Thus, the present study included these groups with the addition a demographically similar control group without a history of any drug or alcohol abuse or addiction.

A battery of sensitive and specific instruments was assembled to measure dimensions of ECF previously tested in heroin addicts with polysubstance abuse to begin to isolate correlates of heroin addiction independent of other drug use. Task selections also considered brain regions either most highly concentrated with heroin or that were most active after acute administration (e.g., prefrontal cortex, anterior cingulate, hippocampus, nucleus accumbens, and ventral tegmental area [(Chang et al., 1997; Galynker et al., 2000; Hakan et al., 1989; Kiyatkin, 1994; Koob et al., 1986; Tanda et al., 1997; Wise, 1989)], as well as studies cited above using tasks with some neuroanatomical specificity to provide direction with respect to identifying the functional correlates of heroin addiction. Thus, response shifting, strategy formation and execution, risky decision making, error monitoring, visual and spatial memory, and complex visual pattern recognition, as well as basic motor acuity and general intelligence, were measured. Although these functions are thought to be affected by psychoactive drugs, the present study sought to determine whether they are differentially or disproportionately affected in the heroin addicts relative to the other study groups.

Hypotheses were threefold. First, based on previous studies including normal control comparisons, it was expected that the three drug groups would exhibit impairments on all neurocognitive measures relative to the control group. Support for this hypothesis would provide initial evidence for the relationship between heroin addiction and neurocognitive function independent of other drugs. It was further anticipated that deficits in heroin addicts relative to the other two drug groups would be specific to the prefrontal cortex. Thus, heroin addicts were expected to exhibit greater disadvantageous decision making and longer deliberation times during decision making (see Rogers et al., 1999a) and less efficient response shifting (e.g., Madden et al., 1997), related to studies of affective impulsivity, than the alcohol group. Also, we hypothesized that heroin addicts would show deficits in processing time,

episodic memory/new learning, visual pattern recognition, problem solving, and cognitive flexibility that are less severe than those of alcoholics but that may have been masked by significant historical alcohol and polydrug use in previous studies. And finally, we expected the alcohol group to show significantly poorer performance on measures of motor acuity than the heroin group based on the literature showing generalized neurotoxic effects of alcohol. Thus, this study constituted a first attempt to isolate neurocognitive deficits that may be uniquely found in 'pure' heroin addicts relative to controls and alcoholics without the confound of a history of multiple drugs of abuse.

2. Methods

The study was conducted in Russia at the St. Petersburg Pavlov State Medical University where control subjects were examined, and at the Leningrad Regional Center of Addictions (LRCA) where heroin addicts, alcoholics and heroin addicts + alcoholic patients were studied. Prior to beginning the study, the United States (US) and Russian study teams met to assess the treatment milieu, establish protocol procedures, and conduct training on the administration of the neurocognitive tasks. Additionally, the status of a small sample of patients' drug abuse was evaluated using a short survey to demonstrate that measures routinely used at the LRCA accurately portrayed drug abuse histories. The results confirmed that sufficient numbers of patients used only heroin, or alcohol, or heroin plus alcohol and self reported reasons for their drug of choice (to be reported in a forthcoming paper) were queried to better understand Russian perspectives that may underlie their drug use patterns.

One Russian psychologist and four psychiatrists were trained to run neurocognitive tasks and administer psychological tests. All task instructions were carefully translated into Russian and back translated into English for quality assurance by two independent interpreters and compared across versions. Neurocognitive testing of patients and control subjects took place over a two-year period from 2003–2005. Procedure monitoring and data collection was performed on a quarterly basis by US research staff. Translators accompanied investigators on each trip, and one Russian interpreter was responsible for data entry and management for conversion of test scores from Russian to English.

2.1 Participants

One hundred heroin addicts, 102 alcohol dependent patients and 60 heroin + alcohol dependent patients at the LRCA were tested; 160 control subjects were tested at Pavlov Medical University. Subjects were between the ages of 18 and 40. The LRCA is a 280-bed hospital for the treatment of alcoholics and drug addicts, 80% to 90% were occupied by alcoholics and 10% to 20% by heroin addicts. Typically, alcoholics and drug addicts remain in the hospital for one month for treatment of withdrawal and detoxification (approximately 7–10 days), any related psychiatric and somatic problems, and inpatient stabilization and initial rehabilitation. Substance abuse treatment included individual and group cognitive and behavioral relapse prevention therapy. Most alcoholic patients are assigned employment within the vicinity of the LRCA and work Monday through Friday. They leave the LRCA in the morning and must return by 5 PM each night, receiving a breathalyzer test upon their return. Heroin + alcohol dependent patients work inside the LRCA during the day. Both groups typically receive counseling sessions in the evenings. All patients from four departments of the LRCA (out of 7) were screened for eligibility. They were provided with the information about the study and only those who were interested and agreed to participate were recruited. All patients signed informed consent forms.

For this study, patients were assessed after three weeks of detoxification and stabilization, during the last week of their stay before discharge when they had been weaned from medications (only medications for somatic disorders had not been discontinued). Patients were

excluded if LRCA evaluations indicated Axis I psychiatric disorders, severe head injury, or other sources of serious brain damage to avoid the significant confound introduced by the interaction between cognitive deficits associated with psychiatric disorders and severe head injury. Patients with Axis II disorders were not excluded, however, as this would reduce the subject pool significantly, limiting the feasibility of recruiting a sufficient number of patients. Also, given that AIDS has adverse effects on neurocognitive function, those known to be infected (as per LRCA records) were excluded (Everall et al., 1999).

Control subjects (N=160) without a history of significant drug or alcohol use were recruited from the community surrounding Pavlov Medical University and included factory workers, college students, and the unemployed. Flyers describing the study were distributed to staff and various employment sites and exhibited throughout this community; individuals either called or visited the University to express their interest. Because of the known age differences between patient populations of alcoholics and heroin addicts in Russia, control subjects were selected to match both the alcoholic and heroin addict groups according to age and other demographic characteristics and then combined for analyses. Thus, controls had a similar range of background characteristics to the addict groups in age, education (higher education after high school is generally received by all citizens in Russia), neighborhood of residence, and overall demographic mix. Control subjects received the same screening and test batteries administered to patients as described below and were subjected to the same exclusionary criteria.

2.2 Screening Procedures

Two levels of screening all subjects prior to participation were performed by Russian study staff. First, for patients, a record check of the LRCA's current files containing assessments conducted upon intake for present hospitalization indicated whether the patient was eligible in terms of current psychiatric status (no dual Axis I diagnoses) using the ICD-X, drug abuse history, indications of HIV status (negative, if available), age and head injury (none severe). The Raven's Colored Progressive Matrices (RCPM, Raven et al., 1938, 1996) were also used to exclude those with mental retardation (<80 estimated IQ) and to estimate general intelligence for all participants. This test was chosen due to its simplicity, nonverbal format, and culture-fairness. Importantly, this task is often used for patients with difficulty understanding English. The RCPM is considered to be a reasonable measure of general intellectual ability and is adaptable to administration in non-English-speaking individuals.

Second, patients were administered two questionnaires to evaluate drug use histories. A questionnaire coined the "DATASI" was developed by combining relevant items from the Addiction Severity Inventory (ASI: McLellan et al., 1992), the Drug Abuse Treatment Outcome Study (DATOS: Hubbard et al., 2003) and additional study-specific questions (available scoring routines for these tests were not used). The Time Line Follow-Back (TLFB) instrument extensively probed about their prior drug use by assessing alcohol (in standard drinks or grams of pure ethanol) and substance use over a specified period of time (Sobell and Sobell, 1996). Drug use histories in the larger patient pool were then evaluated to screen out (i) heroin addicts with histories of significant alcohol or other drug consumption, (ii) alcoholics with significant use of any other drug, and (iii) controls with excessive use of alcohol (including binge drinking) or other illicit drugs. Drug use exclusion criteria for each group, based on information gleaned from these instruments, is as follows:

- *Heroin addicts* who have used alcohol extensively in their lifetime (>100 grams or 3.5 ounces per week on average and/or >100 grams in a single occasion more than once a month).
- *Alcoholics* who have used other illicit drugs more than 10 times during their lifetime.

- *Heroin+Alcohol group* excludes those who have used other illicit drugs more than 10 times during their lifetime (e.g., ephedrine, marijuana).
- *Control participants* cannot exceed alcohol intake of >100 grams pure ethanol per week (3.5 ounces) on average and/or >100 grams pure ethanol in a single occasion more than once a month and/or use of illicit drugs more than 10 times during their lifetime.

Subsequently, patients who met eligibility criteria were recruited and were informed of all aspects of the study prior to obtaining written consent.

2.3 Psychiatric, Psychological, and Contextual Measures

Several psychological and psychiatric instruments were included both for screening purposes and to provide characterizations of groups for further elucidation of differences. These tests are often conducted by LRCA at intake for various study purposes, and permission was granted by consenting patients to the US study team to confidentially review their files. Axis I disorders were excluded by the structured interview for ICD-X, an international analog of DSM-IV. The Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993) and the Cattell 16 Personality Factor Assessment was administered to the substance dependent groups and controls. Each participant's general psychiatric functioning was assessed by a psychologist or psychiatrist using the DSM-IV Global Assessment of Functioning scale (GAF; DSM-IV-TR, 2000). Specific contextual factors extracted from the Drug Abuse Treatment Outcome Study (DATOS; Flynn et al., 1997) interview and incorporated into the DATASI were assessed, including demographic and other background information including health characteristics, education, employment, and mental and physical health status.

Immediately prior to neurocognitive testing, a motor screening test (MOT) was administered to familiarize participants with the use of a computerized task using a touch screen, and to identify any potential differences between groups in general motor acuity. Latency in this task is the primary variable and is defined as the time taken for the participant to touch a cross after it appeared in various locations on the monitor. The arithmetic mean was calculated from the latencies of the ten crosses presented to which the subject correctly responded. Latency was measured in milliseconds.

2.4 Neurocognitive Testing

Three neurocognitive tasks from the CANTAB (CeNeS PLC, Cambridge, UK; Robbins et al., 1994,1998) and three programmed using E-Prime were chosen to measure frontal cortically-modulated functions that are conceptually consistent with the phenomenology of alcohol and other drug abuse. The CANTAB test battery (2004) included measures of visual recognition memory, pattern recognition, problem solving and strategic planning and the E-Prime battery included the Stroop Color/Word Interference, Cambridge Decision Making (CDMT), and the Stop Change Tasks (SCT) (described below). All tasks required behavioral, not verbal, responses to avoid culture and language bias and careful instructions were translated into Cyrillic and carefully recited and explained to participants prior to task initiation.

2.4.1 CANTAB: Delayed Matching to Sample (DMS) The DMS is a test of working memory and pattern recognition including variable delays between presentations of visual stimuli (see Kempton et al., 1999 for task description). The stimuli are complex patterns made up of four sub-elements each of a different color. One of the choices is identical to the sample, one is a novel distractor, one has the shape of the sample and the colors of the distractor, and the fourth has the colors of the sample and the shapes of the distractor. All choices have one quadrant in common with the sample to discourage strategies based on encoding single quadrants of the sample. There are 40 counterbalanced trials consisting of five simultaneous

presentations of sample and choices, and five trials each of 0 second delay, 4 second delay, and 12 second delay. The “simultaneous” trials measure simple pattern recognition. Delay presentations involve working memory and require mastery of pattern recognition in order to perform accurately. Outcome measures include latencies to respond and percent correct during simultaneous and the total delay presentations. The DMS task also provides a variable based on signal detection theory that indicates the probability of an error given an error. Scores range from -1.00 to $+1.00$ with lower scores indicating that many errors are being made in general, while higher scores indicate that subjects are likely to make errors only if they have just made an error on the previous trial. Within the context of DMS performance this score can be thought of as the strength of the emotional reaction to making an error that, in turn, generates another error immediately following. This score is not, however, considered a central measure of pattern recognition or working memory.

2.4.2 CANTAB: Paired Associate Learning (PAL) This task assesses visual episodic memory and new learning (Robbins et al., 1997). Boxes are displayed on the computer screen one at a time in a random pattern. One or more of the boxes contain patterns. There are eight stages within which a different number of patterns are displayed in boxes that are opened one at a time. The subject must touch the empty box where the pattern was originally located. If the subject makes an error, the patterns are presented again to remind the subject of their locations. When the subject gets all locations correct, s/he moves onto the next stage which becomes more complex with an increasing number of patterns within the boxes. If the subject cannot complete a stage correctly, the stage is terminated. Outcome measures of interest are the mean errors to success, mean trials to success, and stages completed.

2.4.3 CANTAB: Stockings of Cambridge (SOC) The SOC is a spatial planning and problem solving task based on the Tower of London (Shallice, 1982). Two displays each containing three colored balls are presented on the computer screen. The displays are analogous to stacks of colored balls held in stockings or socks suspended from a beam. The participant must touch the balls in the lower display to copy the pattern of balls in the upper display. Balls may be moved one at a time by touching the ball then touching the position to which it should be moved. The task consists of problems requiring 2, 3, 4, and 5 moves to copy the upper display. Problems solved in the minimum number of moves and the mean number of moves for problems 2 through 5 combined on the SOC are considered the central measures of planning and problem solving abilities.

2.4.4 E-Prime: Cambridge Decision Making Task The Cambridge Decision Making Task (CDMT) was developed to dissect cognitive abilities believed to affect risk taking as defined by selecting an unlikely large reward associated with an equally large penalty rather than a likely small reward/penalty, a form of affective impulsivity (Rogers et al., 1999a; 1999b). It has been consistently shown to activate the OFC in normal controls (Rogers et al., 1999a) and to generate lower levels of anterior cingulate activity in drug addicts (Fishbein et al., 2005). This task is described in Fishbein et al. (2005); the only difference was the conversion of points to rubles. Initially, 3000 rubles are presented on the computer screen to begin the task and participants were told that the computer has hidden, on a random basis, a ring inside one of 6 yellow or blue boxes arrayed on the screen. The goal is to decide whether this ring is hidden inside a yellow or blue box. The participant is told that each presentation is independent of the one before, as in the roll of die. The choice of options, however, involves gambling a certain number of points (represented as rubles) associated with each choice, with the odds being 300 vs 2700, 600 vs 2400, 900 vs 2100, 1200 vs 1800, and 1500 vs 1500 for the blue vs yellow choice. The ratio of colored boxes (5:1, 4:2 and 3:3) and the balance between the associated rewards vary independently from trial to trial according to a fixed pseudorandom sequence. While the point structure is fixed for each stimulus presentation, the probability of

a win or loss is a function of the number of blue versus yellow boxes presented. On all trials with an unequal ratio of yellow and blue boxes (e.g., 5:1 or 4:2), the larger reward is usually associated with the least likely outcome, thus capturing the conflict inherent in risk-taking situations. If the correct color is chosen, the points associated with that choice are added to the total score; if the wrong color is chosen, the same points are subtracted. The total number of points gained or lost is displayed after each trial. No monetary value is attached to points accumulated by the end of the task. Performance measures generated include percentage of choosing the least likely outcome (i.e., percent total high risk choices) and mean deliberation times as a function of the balance of risks and rewards.

2.4.5 E-Prime: Stop Change Task The Logan Stop-Change Task measures an aspect of inhibition that involves the ability to shift responses in light of new information (Logan & Burkell, 1986), a function which have been shown to activate the right hemispheric anterior cingulate cortex, supplementary motor area, and inferior prefrontal and parietal cortices, which modulate error monitoring, interference control, and task management (Rubia et al., 2001). The task consists of two parts: (1) the baseline (36 trials) to assess the participants' choice reaction time and (2) the main task (96 trials) to assess the participants' ability to inhibit a prepotent response and initiate a new response. Each of these parts included (a) instructions in which all possible screens were slowly displayed and explained, (b) several practice trials to ensure that the participants understood the instructions, and (c) either the actual baseline or actual main task.

In the baseline portion, participants must press the "1" key when a star is displayed on the screen or press the "3" key when a circle is displayed. The baseline reaction time is calculated as the average reaction time for all correct responses to the 36 baseline trials. Feedback is provided after each trial and the message "too slow" is displayed in a red square if the participant makes no response within 1800 milliseconds after the imperative stimulus is presented.

The main task was identical to the baseline task except that participants were instructed to press the "2" key when they heard a tone rather than the "1" or "3" key as above. Tones were presented in 25% of the trials at four different intervals following the imperative stimulus (i.e., the star or circle). Three trials in each block presented a tone at 100 milliseconds before the expected key press; on these trials, it was relatively easy to stop the prepotent response (i.e., to press either the 1 or 3 key) and initiate the new response (i.e., to press the 2 key). Three trials in each block presented a tone at 500 milliseconds before the expected key press based on the baseline trials; on these trials, it was almost impossible to stop the prepotent response and to change to the new response. Three trials in each block also presented tones at 250 milliseconds and at 350 milliseconds each; these six trials were of intermediate difficulty.

The need to respond as quickly as possible was emphasized. This emphasis was made to minimize the chance of participants later adopting a strategy of slowing down to listen for the tone in the main task. The "too slow" message was added to this task to minimize the likelihood of participants responding too slowly during the main task. Measures from this task include percentage correct for all trials combined and each trial type separately (i.e., tone delay of 100, 250, 350, 500 msec).

2.4.6 E-Prime: Stroop Color/Word Interference Task As most drugs of abuse are thought to influence function of the anterior cingulate, the Stroop Word/Color Interference Task was included (Bench et al., 1993; Pardo et al., 1990). This task uses previously learned information so that all three attributes of executive frontal lobe function can be assessed: (1) complexity; (2) a "nonroutine" nature; and (3) the novel use of old information. The Stroop first presents color words printed in the color that the words spell are presented (neutral

condition). In the second stage, a series of Xs are presented in the same three colors (congruent condition) and in the third stage (incongruent condition), words are presented in colors that differ from what the words spell (e.g., the word blue is presented in red). A correct response is recorded when the subject indicates with a key press the color rather than what the word spells. If an error is made, the subject must correct the response. Measures generated for this task are the Word Score and Color Score, reflecting the total number of responses completed in 45 seconds for each form, and the Predicted Color-Word Score. The central measure “interference” derives from these scores and is calculated by multiplying the first two conditions and dividing that product by the sum of those conditions to produce a “CW prime” score ($W \times C / W + C = CW'$). The sum of third condition is then subtracted by the CW' score ($CW - CW' = \text{interference}$).

2.4.7 Statistical Analyses—Data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 14. Frequencies and means were determined for demographic and drug use variables. One way analyses of variance (ANOVA) were used to explore group differences in age, marital status, education, BPRS scores, GAF scores, and self health ratings. Subsequently, GLMs using Tukey’s *post-hoc* tests thresholded at level $p < 0.05$ were run to identify specific pair-wise differences in background measures. Multivariate general linear models (GLMs) were also used to examine differences among groups in cognitive performances. Because age was significantly different among the groups, it was included as a covariate in all analyses. After identifying main effects from the GLMs, pair-wise comparisons were evaluated using Tukey’s *post-hoc* tests thresholded at level $p < 0.05$ to identify the source of group differences. For each comparison we also calculated effect size in terms of Cohen’s (1988) difference in the means divided by its pooled standard deviation; effect sizes in bold indicate Tukey-adjusted statistical significance. In order to account for 5 variables in the DMS task, 3 variables in PAL, and 2 variables in SOC, we used additional conservative Bonferroni adjustment; adjusted p-values for these analyses are reported.

3. Results

Tables 1 and 2 contain demographic and psychological information and drug use histories of the heroin addicts, alcoholics, heroin+alcohol dependent patients and control subjects. Main effects for age were significant ($p < 0.0001$). Pairwise comparisons showed significant differences in age between each group pairing with the exception of heroin addicts and the heroin+alcohol group; alcoholics were older than control subjects ($p < 0.0001$; which included age-matched controls for all three drug groups), and the heroin ($p < 0.0001$) and heroin+alcohol ($p < 0.02$) groups were younger than the controls. Marital status was also significantly different between controls and the heroin addicts ($p < 0.01$) and the heroin+alcohol group ($p < 0.001$) but not from the alcoholics; controls and then alcoholics were more likely to be married. Controls also were more likely to have attended college than alcoholics ($p < 0.007$), heroin addicts ($p < 0.012$) and heroin+alcoholics ($p < .0001$), however college attendance was relatively high for all groups, particularly the alcoholics; citizens in Russia are generally required to obtain higher education of some type (including trade school) after high school. Controls had the highest rate of having a full time job than heroin ($p < 0.003$) and heroin +alcohol ($p < 0.0001$) groups but did not differ from alcoholics. All three drug groups reported higher ratings on the BPRS than the controls, as expected ($p < .0001$), however, heroin addicts and the heroin+alcohol group reported similar ratings. Control subjects generated the highest Global Assessment of Functioning scores which were significantly different from all three drug groups ($p < .0001$ each) while alcoholics and the heroin+alcohol groups had similar scores. Interestingly, controls and alcoholics reported the highest self health rating with alcoholics scoring higher than controls, albeit not significantly. The potential moderating effects of these background variables were examined by including them as covariates in the GLM analyses of cognitive data; the primary findings, detailed below, were not altered. Also, self-reported HIV

status (49 patients reported being positive) was examined in the context of neuropsychological functioning and no relationships were significant (self-reported AIDS during screening was exclusionary).

With respect to drug use histories, heroin addicts tended to initiate alcohol use before the other groups followed by the heroin + alcohol group. The heroin + alcohol group used alcohol for fewer years than the alcoholics due to their prior years of exclusive heroin addiction. Similarly, the duration of heroin dependence differed between these heroin addicts and the heroin + alcohol group due to their replacement of heroin with alcohol. The control group reported substantially fewer relatives with a history of alcoholism than the drug groups.

3.1 Neurocognitive Assessments

The data are presented as the group means and standard errors. We also show the effect sizes that are significant without Tukey multiple comparison adjustment and bolded effect sizes remain significant after the adjustment (Table 3). Because some tests involve more than one variable we have highlighted those that also remain significant after additional Bonferroni adjustment for multiple tests. Most of the significant effects are of medium size according to Cohen (1992); i.e., from about 0.5 to 0.8, although for SOC we observe significant effect sizes around 1.

3.1.1 Raven's Progressive Colored Matrices—Raven's PCM raw scores were converted to percentile ranks using the Raven manual norms for adults. Both age ($F_{4,421} = 19.8, p=.001$) and group ($F_{4,421} = 59.6, p<.001$) were significant factors in Raven's percentile scores although the F statistics show that the group effect predominated. The heroin group performed at the 92.6% (± 9.3) level. The control group performed at the 97.8% ($\pm 3.2\%$), the alcohol group's mean percentile rank was 84.8% ($\pm 10.6\%$) and the heroin + alcohol group's rank was 87.3% ($\pm 8.3\%$). Pair-wise comparisons revealed that the heroin addicts differed significantly from all three groups ($p<.0001$), with heroin addicts producing higher scores than alcoholics and the heroin+alcohol group and lower scores than controls. The heroin+alcohol group did not differ from alcoholics ($p<.702$). Due to these group differences, statistical adjustments were made for IQ in each of the analyses; however, the addition of IQ did not alter the results. Thus, IQ was included as one of the neuropsychological outcomes rather than as a covariate.

3.1.2 Motor Screening Task—An overall group effect was observed on this measure of general motor ability as all drug groups differed from controls ($F=11.36; p<0.0001$). Heroin addicts (mean=835 msec, $sd=253$) specifically showed significantly lengthier response times than controls (mean=731 msec, $sd=191$). The RTs of heroin addicts, however, were shorter than the alcoholics who had longer response times than the other 3 groups (mean = 911 msec, $sd = 272$). There were no differences between heroin addicts and heroin+alcohol patients.

3.1.3 Delayed Matching to Sample—Overall, the three drug groups had fewer correct responses on DSM simultaneous and delay measures relative to controls (see Table 3). The alcoholics also responded with significantly longer latencies for both stimuli types. Compared to alcoholics heroin+alcohol group had longer latencies for the simultaneous items but shorter latencies on the delay trials, however additional Bonferroni adjustment for testing 5 variables makes the effect insignificant. Heroin addicts, on the other hand, performed more poorly than controls in terms of correct responses, but also exhibited shorter latencies on both simultaneous and delay trials than the alcoholics. Also, latencies for both trials in the heroin+alcohol group were longer than the heroin group but shorter than the alcoholics (although after the multiple comparison adjustments, the differences between heroin addicts and controls were of insufficient magnitude). Given the motor acuity results showing significant differences

between controls and all three drug groups, with alcoholics performing the worst, analyses for the latency variables were rerun to include motor responses as a covariate. The initial results were virtually unchanged.

On the variable “strength of the probability of an error given an error”, the control group had the lowest mean score ($-.73 \pm .04$) and the heroin group had the next lowest score ($-.58 \pm .06$), followed by the alcohol group ($-.44 \pm .06$) and the heroin+alcohol group’s score ($-.48 \pm .07$). These differences were strongest between the controls and both the alcoholics and heroin+alcohol group. Heroin addicts showed a lesser tendency to commit random errors relative to controls, but committed a greater number of random errors than the alcoholics, although effect sizes suggest these differences were of relatively small magnitude. Insert Table 3 here

3.1.4 Paired Associate Learning—On the PAL, like the DMS task, there were main effects for group for mean errors and mean trials to success, with controls performing better in all cases (Table 3). The alcoholics completed fewer stages than did the controls, and alcoholics performed worse than heroin addicts, although the effect size was low. The heroin+alcohol group differed significantly only from controls on mean errors to success and mean trials to success PAL measures, but not stages completed.

3.1.5 Stockings of Cambridge—All three drug groups solved a fewer number of problems using minimal moves than the controls and required a greater number of moves for each stimulus presentation combined (moves 2–5), thus the main effect of group was highly significant (Table 3). The heroin group also performed significantly better than the heroin+alcohol group on mean moves 2 through 5 combined, although the effect size suggested that this difference was relatively small.

3.1.6 Cambridge Decision Making Task—The main effect of group was significant for average RTs for high risk choices and for percentage of high risk choices (i.e., in trials where there is greater likelihood of losing than winning points, see Table 3). Heroin addicts exhibited the longest RTs and controls the shortest. Motor acuity values were added as a covariate to adjust for group differences in the RT measure and results were unaltered. As seen in Figure 1, the central measure of percentage of high risk choices was also significantly greater only in the heroin addicts who selected the highest number of risky decisions overall (differences from the control group: Alcohol, $ES=.27^*$; Heroin, $ES=.33^*$; Heroin+Alcohol, $ES=.27^*$; Overall Model, $F=4.15$, $p<.006$).

3.1.7 Stop Change Task—The percentage correct for all responses, including tone and non-tone stimulus presentations, on the four active trials combined was significantly different between groups, as reflected in main effect results. However, only the heroin+alcohol group differed significantly and with sufficient magnitude from the control groups on this measure, showing fewer correct responses. For only those trials that included the 250 msec tone delays (moderately easy), the heroin+alcohol group also performed with a greater percentage of errors than the other two drug groups (although effect sizes were small). On the 500 msec tone delay (the most difficult), all three drug groups responded significantly more accurately than controls. As expected, all groups produced fewer correct answers with the increase in delay, however the controls showed a higher level of performance on the full (both tone and non-tone trials) task but then rapidly declined with the introduction of graduated delays, concluding with only 12% correct at 500ms delay. Conversely, the alcohol+heroin group performed worse than the other groups until 250ms delay when the drop in performance began to decline concluding with only 18% correct responses. See Table 3 for full results. Figure 2 illustrates change in correct responses relative to group: the overall models for % correct responses during 100msec, 250msec and 350msec trials were not significant. During the 500msec trial, however, % of

correction responses did differ between the groups (differences from control group: Alcohol, $ES = -.53^*$; Heroin, $ES = -.40^*$; Heroin+Alcohol, $ES = -.40^*$; Overall Model $F = 7.15$, $p < .0001$).

3.1.8 Stroop Interference Task—For the central “interference score,” the heroin+alcohol group did not differ from the controls in the extent to which they experienced interference with cognitive processing of an incongruent stimulus (see Table 3) while the heroin addicts and alcoholics did differ significantly, however effect sizes were small for the heroin-control comparison. As lower scores are reflective of higher levels of interference, it appears that the alcoholics showed the greatest deficits relative to controls, as reinforced by effect sizes, followed by the heroin addicts. Given that the interference measure is partially a function of reaction time, motor acuity was entered as a covariate in the analyses and the results were slightly altered; the difference between controls and alcoholics remained, however, the difference (irrespective of effect size) between controls and heroin addicts was no longer significant ($p = 0.09$).

4. Discussion

The study described herein included a unique subject population with a known history of only heroin dependence with a limited extent of prior drug or alcohol experience and no current abuse or dependence on other drugs. Our primary results show that these heroin addicts are more similar to alcoholics and patients who use heroin and upon cessation become alcoholics (i.e., heroin + alcohol group) in neuropsychological function than different. However, a few potentially important distinctions emerged that do not appear to be related to background variables, such as age, physical health or education. Also, given that the heroin+alcohol group tended to show scores intermediate to the heroin and alcohol groups, there does not appear to be an additive effect of abusing both drugs over time.

4.1 Interpretations of Specific Task Performance Deficits

All three drug groups showed deficits in general intellectual ability, as measured by the RCPM, relative to control subjects. Of the drug groups, the heroin addicts showed the highest level of performance while the alcoholics performed substantially worse. Alcoholics' scores were not, however, statistically different from the heroin+alcohol group. Age was a factor in level of intellectual functioning with the alcoholics being significantly older than the other drug groups, however including age as a covariate did not alter these results. The fact that, although alcoholics and the heroin+alcohol group did not significantly differ in intelligence, the alcoholics used and were dependent on alcohol for a greater number of years suggesting that the drug of choice may be more influential in our results rather than the duration of use. Given overall group differences, the RCPM was initially included in the model and not shown to influence the results in any way, suggesting that higher order cognitive function (ECF) remains significantly different between the groups irrespective of deficits in subservient intellectual functions.

Similarly, on the measure of general motor ability, each drug group performed worse than the controls, however, alcoholics exhibited the lengthiest response times which is reflective of motor incoordination. Heroin addicts and the heroin+alcohol group were not different in response times. Psychomotor slowing and motor retardation have been attributed to alcoholism (e.g., Ciesielski et al., 1995) but no studies of motor disturbances in heroin addiction, other than simple acute administration effects, could be located. This study suggests that heroin addiction is also associated with motor sluggishness.

All drug groups differed significantly from controls, and for latencies to each other, on our measure of perceptual matching, immediate and delayed visual memory (DMS) and in ability to form visuo-spatial associations (PAL). These related functions recruit structures within the

medial-temporal lobe such as the hippocampus, with input from the dorsolateral prefrontal cortex (DLPFC)(Lamar et al., 2004;Monk et al., 2002;Schon et al., 2004;Tanabe et al., 2005), suggesting that our drug groups have some dysfunction in these interconnected regions. Of note, however, performance of these groups on the basic measure of pattern recognition (DMS) was poorer than the controls, suggesting that more basic deficits exist in functions that are otherwise supportive of working memory. These basic deficits do not necessarily extend to impairments in motor acuity given that adjustments for this measure did not alter the results for either the DMS or PAL.

Nuances in performance on these two tasks provide some interesting contrasts between heroin addicts and the other two drug groups. With respect to delayed visual memory, heroin addicts exhibited the shortest latencies in both trial types and, at the same time, had fewer correct responses. Given that there were no significant differences in correct responses between drug groups and that heroin addicts responded more quickly and less accurately than did the controls, one interpretation is that heroin addicts may tend toward impaired motor inhibitory responding that impedes performance on a working memory task. Longer latencies in the alcoholics, in contrast, suggest less cognitive efficiency. As discussed below, however, impairments found in the heroin addicts are unlikely to be solely attributable to inhibitory deficits given their superior performance on some measures of the Stop Change Task. Unfortunately, attentional mechanisms were not evaluated in this study which may have provided an indication of whether the inability to recognize patterns simultaneously presented was related to a lack of focus. For the central measure of visuospatial learning (“stages completed”), on the other hand, heroin addicts showed a tendency to perform better than alcoholics who completed fewer stages than the other groups. Taken together, the poor performance of these drug groups on both tasks supports previous findings of deficits in learning and memory that may be a function of damage from neurotoxicity to the hippocampal formation in the temporal lobe (Day et al., 2003) which is structurally altered by drug addiction (Nestler, 2002;Robbins and Everitt, 2002).

With respect to the “strength of the probability of an error following an error” variable, all four groups responded with a predominance of random errors not related to performance on previous trials, suggesting that error-proneness characterizes each of our groups. Controls responded with the most random errors followed closely by the heroin addicts and lastly the alcoholics and heroin+alcohol group. No group produced positive numbers, however, which would reflect a tendency to experience interference from the emotional reaction to making an error, leading to additional errors. In light of findings that controls performed with less response shifting on the SCT and also made the greatest number of random errors on the DMS, it appears that disinhibitory tendencies on the part of controls may be a result specifically of reflection impulsivity (see Clark et al., 2006).

All three drug groups showed further impairments relative to controls on the test of frontally-modulated (particularly DLPFC but also anterior cingulate) problem solving abilities (SOC). Heroin addicts exhibited better performance than the heroin+alcohol group in that they required significantly fewer moves. Alcoholics did not perform better or worse than the other two drug groups, but showed deficits relative to controls. These findings are consistent with evidence for prefrontal dysfunction in alcoholics and drug addicts (Ersche et al., 2005;Paulus et al., 2002), particularly within the DLPFC shown to modulate problem solving and spatial planning on similar tasks (Baker et al., 1996;Manes et al., 2002), and correspond well with performance decrements found in learning and memory (e.g., DMS and PAL) in the present study. These skills (as measured by stages completed) in heroin addicts, on the other hand, appear to be somewhat less dysfunctional than in the other drug groups.

Relative to our original hypotheses, perhaps the most noteworthy group difference was that heroin addicts showed a distinctive pattern of performance on the CDMT, a measure of

affective impulsivity in decision making. In the present study, heroin addicts selected a significantly greater percentage of disadvantageous or risky options and exhibited the lengthiest reaction times during high risk choices relative to controls. The other two drug groups selected a greater number of risky choices than the control group, although differences had a small effect size. Control subjects showed the shortest RTs, a finding consistent with Rogers et al. (1999a). Intuitively, one would surmise that the longer the reaction time, the greater the time would be for advantageous deliberation of choices and consequences. But instead, heroin addicts who deliberated longer made riskier decisions and exhibited worse behavioral outcomes. Disadvantageous decision making in conjunction with lengthier reaction times may therefore be indicative of both the difficulty in and quality of decision making under these circumstances that may alter processing of salient stimuli.

Of relevance, two studies reported significant decrements on the CDMT in amphetamine users and MMT patients relative to opiate users (Ersche et al. 2005; Rogers et al. 1999a) while the present study found greater impairment in heroin addicts relative to alcoholics. Together, these findings suggest that decision making deficits may be a function of drug type and not recency of drug use. This notion that specific drugs of abuse may confer differential cognitive effects partially supports our findings of decision making performance deficits in heroin addicts greater than alcoholics; excessive alcohol intake appeared not to relate to risky decision making as did heroin abuse. This finding may be a function of either neurotoxic effects or predisposition characteristics that may differ between alcoholics and heroin addicts. In a culture where drinking is commonplace, underlying mechanisms of propensity to alcoholism may differ in their significance relative to those factors (e.g., genetics) that are strongly influential in the US.

Tendencies among these heroin addicts toward poor decision making ability may reflect an affective impulsivity that specifically relates to reward salience. Support for this notion can be found in studies by Kirby and Petry (2004) and Kirby et al. (1999) who reported that heroin (and cocaine) addicts showed significantly greater discounting of the value of a future reward as the delay to that reward increased but alcoholics did not. As performance on the CDMT and similar reward-based tasks has been shown to activate the OFC, an area associated with the coordination between processing of emotional and cognitive stimuli (Bechara et al. 1997; Ernst et al., 2002; London et al. 2000; Rogers et al. 1999a), deficits observed in these heroin addicts may be a consequence of OFC damage either predating or resulting from chronic drug use. Further investigation of the nature and extent of OFC involvement in these deficits among heroin addicts requires more comprehensive and longitudinal assessment of risky decision-making.

With respect to measures of motor inhibition and response shifting generated by the Stop Change Task, the data produced mixed results. As expected, controls showed superior overall performance on the summary measure of this task; however, they were significantly different only relative to the heroin+alcohol group. Also, the heroin+alcohol group had greater difficulty than the other two drug groups on the moderately easy delay trial. The trend observed for this dual drug use group to respond poorly to both non-delay and delay trials on all measures relative to other drug groups, and in 4 out of 5 measures relative to controls, suggests a possible additive association between using heroin plus alcohol and response inhibition/flexibility.

In marked contrast to our original hypotheses, controls displayed less accuracy on the SCT than the drug groups, especially the alcoholics who showed the highest level of performance on the hardest delay trial. Given that controls performed better when all trials, non-delayed and delayed, were considered, it is possible that these particular subjects were more error-prone specifically for trials that involved response shifting and not for those simply requiring motor inhibition. Although not many studies of cognitive function in heroin addicts and no studies of those who have used almost exclusively heroin have been conducted, one study of heroin

addicts with a history of polydrug use reported less impulsivity relative to users of other drugs not attributable to acute drug effects (Bornova et al., 2005). In contrast, the majority of previous studies find support for impulsivity in heroin abusers when compared with normal controls but they did not address their comparability with other drug use groups and distinguished between various types of impulsivity (Kirby et al., 1999, affective/reward salience; Lee et al., 2005, behavioral/motor; Pau et al., 2002, cognitive). This finding is also in apparent contrast with the primary DMS results in the present study showing increased errors and shorter response times in heroin addicts which appear to be related to disinhibitory tendencies. The SCT is a difficult and often frustrating task. It is possible that the inpatient setting, with addicts who have intrinsic motivation to show behavioral improvement, was more conducive of concentrated play.

Finally, heroin addicts and alcoholics demonstrated less cognitive flexibility and conflict monitoring on the Stroop Interference Task than the control group while the heroin+alcohol group did not significantly differ; alcoholics performed particularly poorly and effect sizes suggest that the decrements in heroin addicts may not be functionally significant. Also, these results may be influenced by impairments found in basic motor function; however, significant differences between control subjects and the alcoholics, who had the poorest motor acuity, remained intact after adjustments were introduced. Thus, although motoric sluggishness may play a role in these Stroop findings as well as in the central measure of motor responsivity, it likely does not provide a full explanation for difficulties the heroin addicts exhibited in shifting attention to salient stimuli and inhibiting an initial tendency to respond.

The overall pattern of findings in this study pertaining to inhibitory tendencies suggests that these heroin addicts are prone to affective impulsivity as measured by the CDMT while behavioral or motor responsiveness were variable depending on the task demands; i.e., in heroin addicts, relative deficits were found in pattern recognition that requires attentional focus (DMS) and ability to suppress irrelevant information and inhibit an initial response (Stroop) while response shifting in response to new information (SCT) was relatively intact. It appears from our findings and those of additional studies discrepant from one another that further subtyping of the concept impulsivity, beyond motor and affective, may be warranted. Higher order cognitive abilities, and not simply motor control, are required for performance on all three tasks that may be more centrally responsible for these group differences.

4.2 Final Remarks

In comparison with other drugs of abuse, there has been substantially less research into neuropsychological deficits in heroin addicts and existing studies are somewhat discrepant in their findings (Rogers and Robbins, 2001), in part due to variable comparison groups, from healthy controls to amphetamine abusers to MMT patients, and in part due to the focus on different functions. In most cases, the literature suggests that there is improvement in cognitive function over time with abstinence (Guerra et al., 1987), however, some reports suggest that this appears to be less true for heroin addicts (e.g., Papageorgiou et al., 2004). The present study, using a broad battery of neurocognitive tests including those considered to be sensitive measures of frontal lobe functioning as well as subservient functions such as intellectual and motor abilities, has shown that in most cases, heroin addicts are similar to alcoholics in their presentation of several marked deficits relative to controls. Thus, common mechanisms may be at play. A strong family history of alcoholism and drug abuse in all three drug groups, for example, is one reasonable explanation for these profound decrements in neurocognitive functioning. Alcoholics were also older, although the average age of these groups was lower than subjects generally included in US studies and controls for age did not alter the results. Interestingly, impairments were remarkable despite the relatively short duration of dependency on drugs and/or alcohol. Alcohol and heroin are similar with respect to several of their

mechanisms of action and neurotoxic effects, including alterations in grey and white matter, structure and function of the hippocampus, amygdala, nucleus accumbens, anterior cingulate cortex, and OFC among others, and perturbations in neurotransmitter (particularly dopamine) responses and metabolism throughout the mesocorticolimbic system (Alexander-Kaufman et al., 2006;Daglish and Nutt, 2003;Koob and Ahmed, 2004;Schlaepfer et al., 2006;Schmidt et al., 2005). Thus, our results showing more similarities than differences between drug groups are perhaps not surprising.

On the other hand, deficits observed in alcoholics were more pronounced than in either drug group. Drug-specific explanations include the severity of alcohol intake over time from a relatively young age, the even higher percentage of alcoholics with first degree relatives with alcoholism relative to the other groups, and the possibility that recovery of function after abstinence from alcohol may be slower than for heroin. The one exception to the severity of impairments found in the alcoholics is our finding of greater risky decision making and reduced deliberation times in the heroin addicts relative to other groups. A few very recent studies were located that found differences in tasks that probe OFC activity in alcoholics (Fein et al., 2004;Mazas et al., 2000), and one study (Dao-Castellana et al., 1998) reported alterations in the function of other PFC structures (e.g., DLPFC) but specifically *not* OFC in alcoholics. It is important to note that most studies of addicts suggest that their drug use “affects” cognitive function even though baseline measures are not available. Such interpretations are, thus, inappropriate given that some level of impairment may antedate and perhaps contribute to the development of drug abuse. In the absence of longitudinal studies it is impossible to discern whether these differential deficits predate or result from use, particularly in light of evidence that ECF dysfunction is more prevalent in adolescents who are at high risk for substance abuse (Fishbein et al., 2006b;Tarter et al., 2003). This restriction on interpretation also applies to the present study. Nevertheless, the neurotoxic effects of heroin are likely to have a more direct relationship with the lifetime usage patterns and thus drug groups are likely to be distinguishable by level of neurocognitive functioning.

One limitation of this study is that patients were tested at three weeks post-detoxification, limiting our ability to generalize to longer periods of abstinence. There are conflicting findings about the duration of cognitive deficits and some functions may improve over time. On the other hand, a recent PET study conducted by the first author found persistent deficits in drug abusers after over 3 months of abstinence primarily in complex executive functions, but not simple abilities such as those measured by continuous performance tasks (Fishbein et al., 2005). It will also be instructive to assess the moderating influence of personality and psychiatric disorders as well as the potential for distinctive cultural influences on cognitive dysfunction among heroin addicts (Pau et al., 2002). Future studies may be particularly informed by the inclusion of Antisocial Personality Disorder (ASPD) which is prevalent in substance abusers and has been repeatedly associated with ECF deficits (Stevens et al. 2001). The possibility exists that inclusion of this construct may alter the results if group differences in ASPD are present. In conclusion, with replications and further elucidation of these results, the design of more effective treatments and perhaps even preventive interventions for heroin addiction may benefit from a focus on decision making abilities and affective impulsivity.

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Figure 1.
Group Differences in Percentage of High Risk Decisions

Figure 2.
Group Differences in SCT Percentage Correct for Each Delay Trial

Table 1
Group Descriptions of Demographic and Psychiatric Characteristics

	Control (N=160)	Heroin (N=100)	Alcohol (N=102)	Heroin + Alcohol (N=60)
Age*	28.3 (± 5.1)	25.6 (±4.2)	32.1 (± 5.3)	26.2 (± 4.1)
Gender	122 M (76%)	64 M (64%)	78 M (76.5%)	53 M (88%)
Marital Status-% married*	40.6%	22%	34.3%	11.7%
Education	13.8%	31%	16.7%	36.7%
% dropped high school*				
% college*	67.5%	52%	68.6%	41.6%
% university*	18.1%	13%	6.9%	0
% with FT job*	79.4%	45%	72.5%	40.0%
BPRS total score* (max=126)	17.9 (± 2.4)	19.3 (± .87)	19.0 (± .09)	19.4 (± .88)
GAF total score* (max=100)	90.5 (± 1.5)	83.3 (± 9.5)	77.1 (± 7.8)	75.7 (± 9.1)
Self health rating % good to excellent*	88.1%	87%	92.1%	65.0%

*
p<.001

Standard deviation in parentheses.

Table 2
Comparative Patient and Control Drug Use Histories

	Control (N=160)	Heroin (N=100)	Alcohol (N=102)	Heroin + Alcohol (N=60)
Age 1 st used alcohol	18.5 (±2.4)	16.8 (± 4.4)	17.1 (± 2.9)	16.2 (± 3.6)
Years Alcohol Use	9.3 (± 5.2)	11.3 (± 7.3)	13.8 (± 5.3)	10.2 (± 4.0)
Duration Alc Dep	NA	NA	7.0 (± 3.8)	4.3 (± 2.5)
Prior Tx for Alcohol	NA	NA	.72 (± .5) 71.6%	.55 (± .5) 55.0%
Number hospitalizations for alcoholism	NA	NA	1.95 (± .27)	.78 (± .13)
% 1 ^o relatives alc probs	12.5%	47.0%	64.7%	53.3%
Age 1 st used heroin	NA	19.6 (± 5.2)	NA	19.1 (± 3.9)
Years Heroin Use	NA	6.3 (± 2.5)	NA	6.5 (± 3.2)
Duration Heroin Dep	NA	6.2 (± 2.5)	NA	6.4 (± 3.4)
Prior Tx for Heroin	NA	93.0%	NA	81.7%
Number heroin overdoses	NA	1.6 (± .28)	NA	1.6 (± .21)
% 1 ^o relatives w/drug probs	.6%	11.0%	2.9%	8.3%

Standard deviation in parentheses.

Table 3
Means, Standard Errors (SE) and Effect Sizes (ES) for Group Differences in Neurocognitive Performance

TASK VARIABLES	CONTROL	ALCOHOL	HEROIN	HEROIN + ALCOHOL	Significance for Group Effect
DMS					
% correct-simultaneous	97.1 (±.54)	95.6 (±.73) ES=.26 ¹	94.6 (±.71) ES=.40 ¹	94.1 (±.9) ES=.45 ¹	F=4.9, p<.002
Mean latency for simultaneous trials	2884 (±67)	3492 (±88) ES=-.71 ¹ , -.79 ³ , -.49 ⁴	2818 (±84) ES=.79 ² , .30 ⁴	3071 (±106) ES=-.49 ² , -.30 ³	F=12.8, p<.0001
% correct all delays	88.1 (±.72)	82.4 (±.97) ES=.68 ¹	83.5 (±.95) ES=.65 ¹	83.0 (±1.2) ES=.64 ¹	F=14.6, p<.0001
Mean latency for all delay trials	3658 (±81)	3967 (±109) ES=-.29 ¹ , -.57 ³ , -.45 ⁴	3384 (±107) ES=.26 ¹ , .57 ²	3502 (±135) ES=.45 ²	F=4.8, p=.003
Strength of prob of error after an error	-.73 (±.04)	-.44 (±.06) ES=.54 ¹ , -.26 ²	-.58 (±.06) ES=-.28 ¹ , .26 ²	-.48 (±.07) ES=-.52 ¹	F=6.4, p<.0001
PAL					
Mean Errors to Success	1.11 (±.13)	2.00 (±.17) ES=-.53 ¹	2.10 (±.17) ES=-.59 ¹	2.17 (±.21) ES=-.63 ¹	F=12.04, p<.0001
Mean trials to Success	1.40 (±.04)	1.68 (±.05) ES=-.60 ¹	1.66 (±.05) ES=-.55 ¹	1.70 (±.06) ES=-.64 ¹	F=11.77, p<.0001
Stages completed [a] (max = 8)	8.00 (±.15)	7.92 (±.02) ES=.41 ¹ , .32 ³	7.98 (±.02) ES=-.32 ²	7.97 (±.02)	F=3.1, p<.03
SOC					
Probs solved in min moves+	9.5 (±.15)	7.7 (±2.0) ES=.95 ¹	7.5 (±2.0) ES=.105 ¹	7.6 (±2.4) ES=.100 ¹	F=34.40, p<.0001
Mean moves-2 thru 5 probs	2.02 (±.017)	2.07 (±.02) ES=-.23 ¹	2.04 (±.02) ES=.36 ⁴	2.12 (±.03) ES=-.45 ¹ , -.36 ³	F=3.35, p=.019
CDMT					
Average RT for risky choices	2323 (±86)	2694 (±116) ES=-.36 ¹	2724 (±101) ES=-.38 ¹	2524 (±141)	F=4.15, p<.006
SCT					
Percent correct in full active task	73 (±1)	71 (±1)	71 (±1)	69 (±1) ES=-0.46 ¹	F=3.52, p=.015
Stroop					
Interference Score	12.9 (±.54)	9.32 (±.73) ES=.47 ¹	11.27 (±.71) ES=.27 ¹	11.72 (±.89)	F=4.66, p<.003

DMS, Delayed Matching to Sample; PAL, Paired Associates Learning, SOC, Stockings of Cambridge; CDMT, Cambridge Decision Making Task; SCT, Stop-Change Task; Stroop, Stroop Color-Word Interference Task. GLMs were used with age as a covariate. P-values are Bonferroni Adjusted. Main effects are reported and pair-wise comparisons using Tukey's *post-hoc* tests thresholded at level $p<0.05$ are bolded. In order to account for 5 variables in a DMS task, 3 variables in PAL, and 2 in SOC, we used additional conservative Bonferroni adjustment; adjusted p-values for these analyses are reported. For the PAL number of stages completed, due to the small number of incomplete stages the assumption of normality could be violated. However a Poisson model showed similar result in terms of the direction and statistical significance.

¹ significantly different from controls

² significantly different from alcoholics

³ significantly different from heroin addicts

⁴ significantly different from heroin-alcohol