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Neuropsychological Consequences of Opiate Use

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Abstract Approximately 3.7 million individuals have used heroin and other opiate substances in their lifetime. Despite increasing knowledge of the effects of heroin, it remains the most abused opiate and use among adults has recently increased. The empirical literature examining the neurocognitive effects of acute and chronic opioid use remains limited; however, findings to date suggest that the use of opiates has both acute and long-term effects on cognitive performance. Neuropsychological data indicate deficits in attention, concentration, recall, visuospatial skills and psychomotor speed with both acute and chronic opioid use. The long-term effects of opiate use appear to have the greatest impact on executive functions, including the ability to shift cognitive set and inhibit inappropriate response tendencies. Factors that contribute to addiction and recovery are also discussed, as it is difficult to disentangle the effects of opiate use on cognitive performance from other factors that may affect neurobehavioral measures.

Keywords Opiates · Neuropsychology · Heroin

Opiate analgesics are a class of compounds derived from the opium poppy, *Papaver somniferum*. Opium originates from the Greek word meaning juice, or exudates, from the poppy. Opium has been used for its psychoactive properties longer than any other agent with the exception of alcohol. In fact, references to the use of opiates for both recreational and medicinal use have been documented as far back in history as 4,000 BC. Commonly administered as a vapor or through punctures in the skin, the variability in opium content and its inconsistent rate of absorption resulted in effects ranging from mild analgesia to respiratory depression and death. In 1805, pure morphine was obtained from the poppy plant, which became the standard analgesic administered to patients undergoing any type of medical procedure or simply to combat "nagging pain." The first widespread use of morphine for analgesia occurred during the American Civil War that resulted in a large number of veterans returning home addicted to the substance. In an effort to deal with morphine addiction, a derivative of morphine was synthesized for medical use. Diacetylmorphine, or heroin, was found to enter the brain more quickly than morphine and was subsequently marketed by Bayer as a nonaddictive cough medicine on the basis that it did not contain "addictive" elements like codeine. Quickly recognized as more addictive than morphine, the drug was soon made illegal. It has only been over the last century that empirical investigations have examined the effects of opiate analgesics on brain function.

The term opiate refers to drugs naturally found in exudate, such as morphine, codeine, and thebaine, whereas the term opioids refers to exogenous drugs (natural or synthetic) that bind to opiate receptors and produce agonist effects. Opioids, other than the natural forms derived from the opium poppy are compounds that are either semi-synthetic (modified from natural forms) or synthetic (synthesized from precursor compounds). Endogenous opioid compounds that exert the pharmacologic properties of morphine, acting as an agonist at the opiate receptor, include endorphins, enkephalins, dynorphins, and beta-endorphins. Opioids can be classified by receptor interactions: agonist, partial agonist, mixed agonist/antagonist,

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and pure antagonists. An agonist is a defined as a drug that attaches to a receptor and produces an action that either mimics or potentiates the action of the endogenous compound (endorphins, enkephalins, dynorphins, and beta-endorphins). A partial agonist is defined as a drug that binds to a receptor and exerts only a portion of the action exerted by the endogenous compound or that produces a submaximal receptor response. A mixed agonist/antagonist is defined as a drug that attaches to a receptor producing a weak agonist action, but displaces the more potent agonist, which has been shown to precipitate withdrawal in opiate-dependent individuals. A pure antagonist is defined as a drug that attaches to a receptor and blocks the action of the endogenous compound or an agonist drug. A list of opioid compounds, classified by receptor interaction, is presented in Table 1 (including both generic and trade names). Opioids can also be classified by target opiate receptor: mu, delta or kappa; pain-reducing intensity: moderate or severe; drug half-life: short or long; or pharmacological effects: e.g., analgesia, respiratory depression, miosis, euphoria, reward, constipation.

Mechanism of Action of Opioid Analgesics

The result of injecting, sniffing, or smoking opiates is intense euphoria, often referred to as a "rush," which lasts only briefly and is followed by a couple of hours of a relaxed, contented state. The rush is achieved when opioids bind with opiate receptors, which are found in many regions of the brain. At least three types of opiate postsynaptic receptors have been classified and cloned: mu, kappa, and delta. Activation of the mu receptor produces the strongest analgesic actions and has a high abuse liability. The mu1 subtype is found outside of the spinal cord for central interpretation of pain and the mu2 subtype is found in the CNS and causes respiratory depression, spinal analgesia, bradycardia, physical dependence, and euphoria. Morphine activates both mu1 and mu2 (thalamus/striatum; brain stem; spinal cord) receptors. The delta receptor is considered a weak analgesic, has a low abuse liability, and is thought to modulate activity of mu receptor. The kappa receptor has modest analgesic effects, causes little to no respiratory depression, miosis, or

Table 1 Opioids classified by receptor interaction

Opiate agonists			Opiate antagonists	Opiate partial agonists
Natural	Semi-synthetic	Synthetic		
Opium	DHCplus	Alfenta	Cyclazocine	Buprenex
Morphine	Diacetylmorphine (Heroin)	Alfentanil	Levallorphan	Buprenorphine
Thebaine	Dihydrocodeine	Anileridine	Lorfan	Butorphanol
Codeine	Dilaudid	Carfentanil	Nalmefene	Dalgan
Papaverine	Endocet®	Darvon®	Naloxone	Dezocine
Noscapine	Endodan®	Dextromoramide	Narcan®	Nalbuphine
Paregoric	Heroin	Demerol®	Nalorphine	Nubain®
MS Contin	Hycodan®	Dolophine	Nalline	Pentazocine
	Hycomine	Duragesic	Naltrexone	Stadol
	Hycotuss®	Fentanyl	Revex	Suboxone®
	Hydrocodone	LAAM	ReVia	Subutex®
	Hydromorphone	Leritine	Trexan	Talwin®
	Lortabs	Levo–Dromoran		Temgesic
	Numorphan®	Levorphanol		
	Opana®	Mepergan®		
	Oxycodone	Meperidine		
	Oxycontin	Methadone		
	Oxymorphone	Methadose		
	Palfium®	Pathadol		
	Percocet®	Pethadol		
	Percodan®	Propoxyphene		
	Percolone	Rapifen		
	Roxicet	Sufentanil		
	Roxicodone	Sufenta		
	Tussionex	Tramadol (Ultram®)		
	Vicodin	Wildnil®		
	Zantryl			
	Zydone®			

dependence, and antagonizes mu receptor actions in brain (producing a strong dysphoric response).

The majority of opioid analgesics acting as agonists at the mu receptor have a pharmacologic action which generally includes a reduction or inhibition of neurotransmission (presynaptic inhibition of glutamate release) via alteration of transmembrane ion conductance (increases in potassium, leading to hyperpolarization) and/or calcium channel inactivation (which reduces neurotransmitter release). Neural adaptations such as tolerance, dependence, addiction, and muscle rigidity are thought to occur as a result of the excitatory effects of opiate agonists acting at the mu receptor. Opioid agonists also activate intracellular cascades and induce protein synthesis, which differs for each receptor. For instance, changes in cellular function at the mu receptor produce euphoria and acts as a positive reinforcer, whereas changes in cellular function at the kappa receptor produce dysphoria and acts as a negative reinforcer.

Diagnostic Criteria for Abuse and Dependence

The positive pharmacologic effects of opioids have led to both abuse and addiction among a growing number of users. Opioid abuse is defined as a maladaptive pattern of use leading to clinically-significant impairment or distress that occurs within a 12-month period. As defined by the DSM-IV (American Psychiatric Association 1994), diagnostic criteria for abuse include at least one or more of the following: (1) recurrent use that results in failure to fulfill obligations at work, school, or home; (2) recurrent use in situations that are physically hazardous, such as driving or operating machinery; (3) legal problems resulting from recurrent use; or (4) continued use despite social or interpersonal problems caused or exacerbated by use. Opioid abuse differs from dependence; the presence of compulsive and repetitive use resulting in drug tolerance and withdrawal symptoms at cessation of use are hallmark characteristics of dependence, however, there has been a recent debate over use of the term 'dependence.' Dependence is differentiated from addiction in that the former generally refers to symptoms of physical dependence, whereas the latter indicates a compulsive drug-taking behavior. It has been suggested by O'Brien et al. (2006) that "any harm that might occur because of the pejorative connotation of the word 'addiction' would be completely outweighed by the tremendous harm that is now being done to patients who have had medication withheld because their doctors believe that they are addicted simply because they are dependent."

Similar to abuse, the DSM-IV currently defines opioid dependence as a maladaptive pattern of use leading to clinically significant impairment or distress that occurs within a 12-month period, which includes at least three or more of the following: (1) the development of tolerance by which there is a decreased effect of the initial amount of drug exposure or that an increased amount of the drug is needed to achieve desired psychopharmacologic effects; (2) withdrawal symptoms are present following cessation of use, which included continued drug use to avoid withdrawal symptoms; (3) drug is taken for an extended period of time and at higher doses than originally intended; (4) a persistent desire to reduce or control drug use; (5) significant efforts are made to obtain the substance, use the substance, or to recover from substance use; (6) there is an interference of social, occupational, or recreational activities because of substance use; or (7) compulsive use is continued despite recurring physical or psychological problems resulting from use. Physiological symptoms of withdrawal, from least to most intense or severe, include: craving, anxiety, drug-seeking behavior, yawning, sweating, lacrimation, rhinorrhea, mydriasis, gooseflesh, muscle twitching, anorexia, insomnia, increased pulse, respiratory rate and blood pressure, abdominal cramps, vomiting, diarrhea, and weakness. These symptoms occur within minutes to several days after prolonged, heavy use that has been stopped or reduced or following administration of an opioid antagonist after a period of opioid use.

It is estimated that approximately 3.7 million individuals have used heroin and other opiate substances, and over 119,000 report having used it within the month preceding the survey (NSDUH 2004). Although the demand for heroin remains significantly lower than for other drugs such as cocaine, methamphetamine, and marijuana, the consequences of heroin abuse are such that its use poses significant health and social problems. Despite increasing knowledge of the effects of heroin, rates of heroin abuse among adults has increased slightly after trending downward over the past few years. Data indicate that rates of past-year heroin use were higher among persons aged 18 to 25 (0.3%) than any other age group including those aged 12 to 17 (0.1%) and 26 or older (0.1%). Between 1995 and 2002, the annual number of new heroin users ranged from 121,000 to 164,000, most of who were over the age of 18, and largely male (NSDUH 2004). There has also been a fourfold increase in heroin use for individuals between the ages of 12 and 17 since the 1980s, and statistics indicate that 1.5% of all 10th and 12th graders have tried the drug at least once (NIDA 2004). Moreover, the National Survey on Drug Use and Health (NSDUH) estimates that 379,000 Americans aged 12 or older used heroin in 2005, including 108,000 who used the drug for the first time (SAMHSA 2006). The typical heroin user today consumes more heroin than a typical user did just a decade ago, which is not surprising given the higher purity currently available at the

street level. Evidence suggests that heroin snorting or inhalation is widespread or increasing in those areas of the country where high-purity heroin is available, generally in the northeastern United States. Although the trend toward inhalation has increased slightly over the last several years, the proportion of users who inhale the drug remains at approximately one-third (SAMHSA 2007). This method of administration may be more appealing to new users because it eliminates both the fear of acquiring syringe-borne diseases such as HIV/AIDS and hepatitis, and the historical stigma attached to intravenous heroin use. The increase in average heroin consumption and in the number of individuals using heroin underscores the importance of understanding the effects of opiate use on neuropsychological function.

Neurocognitive Effects of Opioids

Acute Effects

The impact of opioid use in humans has been studied most effectively by applying a number of neurobehavioral measures, including standard neuropsychological tests. In a study designed to examine cognitive and psychomotor effects of opioids, Hanks et al. (1995) administered single doses of morphine, lorazepam, and placebo to 12 volunteer subjects. Cognitive function was assessed using reaction time, number vigilance, immediate and delayed word recall, and the critical flicker fusion test (CFFT). Subjects receiving morphine demonstrated significant impairment after one hour on all memory tests, and scores on the CFFT were reduced for the six-hour observation period as compared to control subjects. The authors concluded that single oral doses of morphine result in minimal impairment of cognitive and psychomotor function. A study by Kerr et al. (1991) used steady-state infusions of morphine to examine changes in cognitive performance and motor control in volunteer subjects. The investigators evaluated performance on encoding and processing of verbal material and verbal recall during three sequential constant plasma concentrations of morphine and a separate saline infusion day in each subject. Morphine plasma concentrations, which approximated the usual therapeutic dose range for analgesia, caused significant impairment in the time required to encode and process serially-presented verbal information in all subjects. The delayed recall of information presented was significantly impaired three hours after the morphine and saline infusions.

Chronic Effects

While several studies of the chronic effects of opiates have been published, they often include study populations that are confounded by the presence of other drugs of abuse. For example, a study by Bruhn and Maage (1975) examined general intelligence and neuropsychological test scores in two groups of drug abusers. Both groups had abused marijuana, amphetamines, and hallucinogens, but only one group had abused opiates, although the length of use was unspecified. The authors interpreted the differences found between groups to be solely attributable to opiate use. No significant differences were found, and general intelligence and all neuropsychological test scores were within normal limits. Rounsaville et al. (1982) compared opiate addicts to a group of demographically-matched normal controls who did not use drugs. Although both groups demonstrated mild impairment on tasks of attention (Trail Making A &B, Digit Symbol Subtest), visual scanning (Visual Search Test), and motor abilities (Grooved Pegboard), no relationship was found between current or past opiate use and neuropsychological performance. In a study by Guerra et al. (1987) investigators compared opiate abusers to a group of normal controls before and after the completion of a one-week opiate detoxification program on measures of attention, memory, and verbal fluency. Significant differences were noted between the opiate abusers and controls at the first time point (prior to detoxification). At the re-evaluation, one week after admission to the detoxification program, the opiate abusers, however, showed improvement on most measures, and no significant differences were noted between the groups.

By contrast, a study by Carlin (1986) found lower scores for opiate abusers than normal control subjects on measures of visuospatial and visuomotor function. A more recent study by Pakesch et al. (1992) compared opiate abusers to normal controls and found that opiate abusers scored significantly below control subjects on a visual memory recall test (Benton Visual Retention Test). Later, Ornstein and colleagues (Ornstein et al. 2000) found that chronic heroin use impaired performance on sequence generation tasks, spatial working memory and visual pattern recognition memory. In a Hong Kong based study by Lee and Pau (2002), investigators reported that individuals classified as ‘ex-heroin addicts’ who had been abstinent from use for three to 18 months performed more poorly on a test of impulse control (qualitative score of the Porteus Maze Test) than control subjects. The authors state that the former heroin users were more reckless, ignored the rules of the test, and lacked an overall plan for solving the task relative to control subjects. Limited subject information was available, such as medication use, enrollment in a maintenance program, or poly-substance abuse diagnoses. Absence of these details make study results somewhat difficult to interpret.

Ersche et al. (2006) compared current opiate users to both current amphetamine users and a group of former

users of either or both substances, as well as a group of control subjects on a range of neuropsychological tests. As expected, the current and former users performed significantly more poorly on tests of spatial planning, paired associative learning, and visual pattern recognition than control subjects. Interestingly, no significant differences were detected between either current amphetamine or opiate abusers and former users, suggesting that the impairments noted likely do not reflect current effects of the drug. One limitation of this study, however, is that 50% of the former drug users had been dependent on both opiates and stimulants, and using both may have exacerbated the negative consequences of drug use.

Rapeli et al. (2006) examined chronic opiate users on a variety of neurocognitive tasks during 'early' abstinence (within five to 15 days) and found opiate-dependent subjects performed significantly more poorly than controls on tests measuring working memory, executive function, and on a measure of fluid intelligence. Scores on working memory and intelligence tests correlated with days of withdrawal, and was interpreted as evidence for transient cognitive deficits early in the abstinence period. It is of note that a large percentage of the study sample reported current use of benzodiazepines (67%) and/or cannabis (33%) at the time of the evaluation, both of which have been shown to affect cognitive function. These findings are in contrast to early reports suggesting that opiate users and controls do not differ in frontal lobe function (i.e., abstract thinking) (Bruhn and Maage 1975) or verbal fluency (Rounsaville et al. 1982). However, recent studies provide a growing body of evidence that chronic opiate use is associated with significant impairment on several dimensions of cognitive functioning.

Effects of Treatment on Neurocognitive Performance

A range of options exist for the treatment of heroin addiction, including medication maintenance programs. Currently, two primary medications exist in the U.S. for the treatment of opioid addiction. Methadone maintenance (MM) currently is the treatment of choice for opiate dependence in the United States (Joseph et al. 2000), due in part to its ability to relieve narcotic craving and suppress opioid abstinence syndrome, and its association with reduced illicit drug use, reduced spread of hepatitis and HIV, and increased employment (Galynker et al. 2000; Kreek 1997). Methadone is a full mu opioid agonist that has been used as a treatment option for opioid addiction since the 1960s (Dole and Nyswander 1965). More recently, buprenorphine, a partial mu opioid agonist, was FDA approved for treatment in 2002. Advantages of buprenorphine as a treatment option for opioid dependence are that it offers less risk of addiction than methadone, and can be prescribed in an office-based setting rather than a clinic or treatment program, which is required for methadone. The Food and Drug Administration (FDA) approved Levomethadyl acetate (LAAM), also a full mu opioid agonist, in 1994. Given concerns for the potential of LAAM to induce irregular cardiac rhythms, however, enthusiasm for LAAM was greatly reduced and was withdrawn from the U.S. market.

There have been some studies conducted that compare the efficacy of these treatments with regard to retention in treatment, minimization of discomfort, temporary abstinence from heroin, and encouragement of social adjustment. To date, few studies are available that document the effects of replacement treatment on cognitive abilities in opioid-dependent patients. The majority of such neuropsychological studies have examined the effects of methadone maintenance on cognitive function, while fewer reports are available that examine buprenorphine and cognition. Brief reviews of the methadone and buprenorphine studies are provided below. Only one report is available that documents a lack of significant effects of LAAM on driving-related skills (such as reaction time; Lenne et al. 2003), but otherwise no data on the effects of LAAM on cognitive performance are available.

Methadone

Studies examining the effects of methadone maintenance on neurocognitive functioning have been limited despite the fact that heroin use, as well as MM treatment, is quite common. Some evidence suggests that alterations in neurocognitive functioning persist in methadone maintenance patients compared to healthy individuals (Carlin 1986; Pakesch et al. 1992). Significant neurocognitive impairments in delayed recall of prose (episodic memory) have been observed in heroin-dependent outpatients as early as three hours after acute methadone administration (Curran et al. 2001). Impairment in performance on measures of psychomotor speed, working and long-term memory, decision making and response inhibition has also been reported following several months of MM treatment (ranging from 5–60 months) (Darke et al. 2000; Mintzer and Stitzer 2002).

Rotheram-Fuller et al. (2004) examined whether opiate dependence, tobacco smoking, or a combination of the two factors was associated with reduced performance on a decision making task (gambling task [GT]) and the Wisconsin Card Sorting Test (WCST) in four groups of subjects: methadone maintained tobacco smokers, methadone maintained non-smokers, non-opiate dependent tobacco smokers, and nonsmokers. Methadone maintained smokers performed more poorly than methadone main-

tained nonsmokers on GT scores; however, no association of tobacco smoking and reduced GT performance was noted in subjects who were not opiate dependent. Interestingly, although not significant, methadone maintained nonsmokers demonstrated the greatest deficits relative to all other groups on the WCST, which raises the question of whether nicotine provides a counteractive effect of methadone on some cognitive processes. Limitations of the study included a small sample size (N=9 per group), lack of documented premorbid performance differences, and lack of "normative" performance on any of the tasks, even in the control non-smoking group.

In a recent investigation designed to differentiate the neuropsychological effects of long-term abuse from the effects of MM treatment, Mintzer et al. (2005) examined performance of currently abstinent, former opioid abusers retrospectively to both MM treated subjects and matched controls. Results indicated that in general, level of performance of the abstinent abusers was between that of the MM subjects and the controls, suggesting that perhaps some recovery of cognitive ability is restored during abstinence, initially hypothesized by Davis et al. (2002). Interestingly, performance on one of the tests of psychomotor speed (Trails A) was slower for abstinent users than the MM treated subjects, which is counterintuitive to a recovery of function during abstinence theory. Limitations of the Mintzer et al. 2005 study included a relatively small sample size, retrospective nature of the comparison, and marginal significance of differences between groups (Mintzer et al. 2005).

Verdejo et al. (2005) examined the differential effects of methadone maintenance, from those of chronic opioid abuse, on cognitive performance. A battery of neurocognitive tests was administered to current MM patients and to a group of abstinent heroin abusers. Despite similar performance on standard neurocognitive tests including the Stroop Color Word Test (interference condition), the Controlled Oral Word Association (FAS) Test, and the WCST, MM patients demonstrated poorer performance on tasks of measure processing speed, cognitive flexibility and visuospatial attention (the Oral Trails and Five Digit Test; Sedo 2004a, b, respectively) when compared with abstinent heroin abusers.

By contrast, some studies have found that performance of MM patients does *not* significantly differ from that of former heroin abusers or normal controls (Appel and Gordon 1976), or that some areas of cognitive function are spared relative to others. In an investigation by Mintzer and Stitzer (2002), the authors reported that patients in long-term MM treatment (45 months) demonstrated similar time estimation and conceptual flexibility as control subjects, despite showing impairments in psychomotor speed, decision making, and inhibitory processing. These findings suggest that some aspects of neurocognitive functioning, such as attention, may be unaffected by long-term MM treatment, while other domains such as learning and memory may be more susceptible to chronic methadone use. In a recent study of opiate abusers enrolled in a methadone maintenance program, Gruber et al. (2006) reported that following two months of treatment, patients exhibited significant improvements from baseline on measures of verbal learning and memory, visuospatial memory, and psychomotor speed with a working memory component. No effect of illicit drug use was observed when the sample was stratified by urine toxicology results, suggesting that improvements in cognitive function were not associated with additional illicit drug use. These results suggest that opiate-dependent subjects exhibit significant improvement in cognitive function, particularly memory, after two months of MM treatment.

Buprenorphine

Unlike methadone, which is a pure, unselective opiate agonist, buprenorphine is classified as a mixed agent, acting as a mu agonist and a kappa antagonist (Reisine 1995). Buprenorphine is currently approved for both sublingual administration alone (Subutex) and in combination with naloxone, an opioid antagonist (Suboxone). Both buprenorphine and the buprenorphine/naloxone (B/N) combination produce long durations of action, which has implications for less than daily dosing in opioid dependent subjects (Schottenfeld 1999; Gross et al. 2001). Given its unique pharmacological profile, buprenorphine has been hypothesized to have a number of advantages over pure mu agonists like methadone. Several investigations have been conducted to compare buprenorphine to methadone (Kosten et al. 1993; Strain et al. 1994; Ling et al. 1996). In general, it has been found that buprenorphine is an effective medication for the outpatient treatment of opioid dependence, and that sublingual doses of 8 mg buprenorphine daily are approximately equivalent to 50–60 mg oral methadone (Strain et al. 2000). Results from a recent clinical study designed to evaluate the dose effects of buprenorphine/naloxone (B/N) indicate that under chronic daily dosing conditions, the omission of several days of B/N results in only minimal subjective discomfort, despite the fact that some greater physiologic effects of withdrawal may be present (Correia et al. 2006). It was concluded that the pharmacologic profile of buprenorphine permits intermittent dosing which is effective for periods up to four days, a vast improvement over other treatments for opioid dependence.

Given that buprenorphine is a partial opioid agonist, the administration of B/N for opioid dependence may result in less impairment of cognitive functions. Strain et al. (2000),

found that acute doses of buprenorphine alone and buprenorphine combined with naloxone produced mild impairment in non-dependent opioid users on psychomotor tasks, which included the Circular Lights and computerized Trail Making test, but not on the Digit Symbol Substitution Test (DSST). In a study designed specifically to examine the effects of buprenorphine on cognitive function, Mintzer et al. (2004) evaluated neurocognitive performance 7–10 days after administration of B/N (doses: 8/2, 16/4, 32/8) in opioid dependent volunteers. Subjects were evaluated prior to B/N administration and at one and six hours after administration. Tasks administered included two computerized Trail Making tests (analogous to Parts A and B of the traditional pencil/paper Trail Making Test, which measure psychomotor speed/cognitive flexibility), a computerized version of the DSST, a time estimation task (a measure of time perception), and measures of working memory/focused attention (the digit recall task, the "n back" task, and a word-memory paradigm with both free recall and recognition memory components). Minimal impairments in cognitive performance were observed, despite a four-fold increase in dose of buprenorphine/naloxone. A significant dose effect was noted for long term/episodic memory performance at the highest dose. However, given that doses of buprenorphine in the 4–24 mg range are the most commonly prescribed, the impairment observed in the present study was unlikely to have implications for most individuals. Although the investigation was conducted using a small study sample (N=7), all subjects were housed on a closed residential unit where concomitant drug use is prohibited, thereby eliminating potential confounds of other illicit substance use. It is of note, however, that a non-drug cohort was not included in the study, precluding the comparison between B/N treatment and normative control conditions. The investigators did compare data from their 2004 investigation to data collected in 2000, which included methadone-maintained subjects and a control subject cohort. The authors found comparable performance between the low dose B/N subjects and the control sample from their earlier study, suggesting that B/N administration does not significantly impair cognitive performance relative to performance in control subjects.

In a recent study conducted by Pirastu et al. (2006), methadone and buprenorphine maintained individuals were compared to non-opiate dependent, drug-free control subjects on tasks of decision-making (GT), general intelligence (WAIS-R), visuospatial performance (BVRT) and cognitive flexibility (WCST). Compared to control subjects, both methadone and buprenorphine maintained subjects performed more poorly than control subjects on the BVRT. Despite similar WAIS-R scores for the opiate dependent subjects, results indicate superior performance in buprenorphine maintained subjects as compared to methadone-maintained subjects on the WCST, which was interpreted to reflect the ability to appreciate long-term consequences in the former group. Interestingly, buprenorphine-maintained subjects performed better than methadone-maintained subjects and healthy controls on all GT measures (number of choices from advantageous and disadvantageous decks, net score). Overall, results from these studies suggest that treatment with buprenorphine may help to improve cognitive performance in opioid dependent subjects relative to other treatments, including methadone.

Other Opioids

Opioid-based medications for treatment of opioid dependence, as well as for the relief of chronic pain, have a high abuse liability. Thus, a major concern is the effects of long-term opioid medication on cognition. It is imperative to consider the results of investigations that have examined the effects of acute and chronic administration of other opioid compounds on neuropsychological performance.

Tramadol

Tramadol (trade name: Ultram) is a partial agonist at mu receptors and blocks presynaptic uptake of both norepinephrine and serotonin, which produces both an antidepressant and an analgesic effect (Gobbi and Mennini 1999; Franceschini et al. 1999). Relative to morphine, tramadol is ten times less strong (Lee et al. 1993), and reports indicate that relative to other opioids often used for patient-controlled analgesia (PCA), tramadol produces less overt sedation, less respiratory depression, and less euphoria (Preston et al. 1991; Lee et al. 1993). Silvasti et al. (2000) compared the use of tramadol to morphine in patients using PCA and evaluated cognitive function, specifically psychomotor speed and visuospatial ability, using the digit symbol substitution test (DSST). The author reported no significant differences in performance between the two groups, although testing was completed within a 24-hour period of the surgical procedure, raising the question of potential residual effects of intraoperative medications on performance. In an investigation designed to examine the cognitive effects of tramadol relative to a much stronger pure opioid agonist, fentanyl, Ng et al. (2006) administered the Mini Mental Status Exam (Cantonese version) and the BVRT to inpatients randomized to receive one of the two opioids via a PCA system. Although no significant differences in performance were detected between groups, significantly more patients receiving tramadol were able to complete testing postoperatively relative to those receiving fentanyl. In addition to the superior analgesic effects, tramadol, relative to other PCA medications such as

fentanyl, may increase motivation to complete demanding cognitive tasks.

In a recent study by Zacny et al. (2005), subjective and psychomotor effects of orally administered tramadol were compared with administration of morphine and lorazepam (Ativan). Although tramadol administration was associated with increased subjective ratings related to abuse ('drug liking' and 'take again'), no psychomotor or cognitive impairments on the DSST task were observed relative to the morphine or lorazepam group. The authors concluded that tramadol is an effective analgesic with abuse liability related effects, that did not produce the same psychomotor impairments seen in the lorazepam treated subjects.

Oxycodone

Oxycodone (trade name: Oxycontin) is a semi-synthetic derivative of thebaine and is a long-acting opiate that has less abuse potential than the short-acting formulations (i.e., codeine). Oxycodone is metabolized to noroxycodone and noroxymorphone, alpha- and beta-noroxycodol, oxymorphone, alpha- and beta-oxymorphol, and alpha- and beta-oxycodol. Oxycodone has been shown to be a weaker μ-opioid receptor agonist than morphine (Lalovic et al. 2006). The indicated use for oxycodone is for moderate to severe pain. It is available in oral form in the U.S. and can be combined with salicylates or acetaminophen. In a study by Zacny and Guitterez (2003), the effects of oxycodone dose on subjective and psychomotor measures were compared with morphine and lorazepam. Cognitive measures included the DSST, a computerized logical reasoning test, an auditory reaction test, a memory test, and hand-eye coordination test. Cognitive impairment was detected on all measures at the high dose of oxycodone, although impairment was less for the oxycodone group relative to the group receiving lorazepam.

Gaertner et al. (2006) assessed cognition and psychomotor function in non-cancer pain patients treated with controlled release oxycodone (CRO) and control subjects, using a computerized test battery developed to assess driving ability, which included measures of attention, orientation, reaction time, concentration, and performance under pressure. Treatment with CRO did not affect overall performance on any of the cognitive measures; however, the *variability* in performance between subjects highlighted the necessity of taking individual assessments. Despite age- and sex-matching control subjects to CRO patients, one limitation of the study was that no information was available for previous treatments or for drug or alcohol-use history. Further, although CRO patients with "severe psychiatric or neurologic disease" were excluded from the study, it is unclear if the same criteria were used in selecting control subjects and by what method medical and psychiatric histories were assessed, either of which could potentially influence the interpretation of the neuropsychological findings.

Morphine

Morphine is a pure opioid agonist, administered orally or intravenously, that produces intense analgesia and sedation. In a study of long-term oral, sustained-release morphine on cognitive function in patients with chronic pain, Tassain et al. (2003) evaluated patients at baseline (pre-administration) and after three, six and 12 months of treatment on measures of inhibition and processing speed (Stroop interference score), information processing, psychomotor speed and alternating set (Digit symbol subtest of the WAIS-R). Relative to a group who stopped taking morphine prematurely, morphine-treated patients performed better on all measures. The authors concluded that morphine treatment does not disrupt cognitive performance, but rather slightly improves cognitive function, likely due to pain relief and management. Furthermore, the lack of cognitive deficits associated with morphine administration in this study may also have been related to (1) administration of a long-acting form of the drug, as opposed to acute morphine administration, which has been shown to disrupt cognitive performance (Cleeland et al. 1996), and (2) the choice of a study sample that consisted of subjects who were not opiate abusers.

Hydrocodone

Hydrocodone (trade names: Hycodan, Vicodin, Lortab, Zydone) is a semi-synthetic derivative of codeine that has both antitussive and analgesic properties (Zacny 2003). Available only in combination with other drugs including aspirin, acetaminophen, and ibuprofen, hydrocodone acts at the mu receptor and is considered one of the more widely-abused prescription opioids in the United States (SAMHSA 2006). Subjective and psychomotor effects were examined in non-opiate abusing individuals administered hydrocodone in combination with homatropine, which is a peripherally-acting anticholinergic. This study was conducted using a double-blind crossover method, in which all subjects received placebo, 5/1.5, 10/3, or 20/6 mg doses of hydrocodone/homatropine (HC/HO, trade name Hycodan), 40 mg of morphine, and 2 mg of lorazepam. The test battery, which included the DSST, a computerized logical reasoning test, an auditory reaction test, a memory test, and hand-eye coordination, was administered at baseline and five hours after dosing. Lorazepam impaired performance on all five measures, whereas the highest dose of HC/HO impaired performance only on the DSST (number of figures drawn, number of figures drawn correctly) relative to placebo. The recommended, commonly prescribed dose of Hycodan

(5/1.5 mg HC/HO) did not result in either subjective or psychomotor impairing effects. Limitations of the study include the absence of a group receiving HC alone, making it difficult to dissociate the effects of hydrocodone from those when a hydrocodone/homatropine combination is administered. In a separate double blind crossover study, recreational drug users received placebo, 5/500; 10/500; or 20/1000 mg doses of hydrocodone/acetaminophen (HYD/ACET, trade name Vicodin); 40 mg of morphine sulfate and 1,000 mg of acetaminophen. Using the same neurocognitive battery, results indicated that 20 mg HYD/1000ACET and morphine impaired cognitive and psychomotor performance, as measured by the number of symbols drawn correctly on the DSST and the logical memory test. Further, hand-eye coordination was also impaired relative to placebo at the 20/1,000 mg dose of hydrocodone/acetaminophen. Morphine was also found to impair DSST, logical memory performance, and auditory reaction time. It was concluded that although increases in the subjective effects suggested increased abuse liability ('take again' or 'liking' of the drug), impairment in cognitive and psychomotor function was only observed at the highest administered dose, which is two to four times the normally prescribed dose. In contrast to the previous study of hydrocodone (Zacny 2003), the present study (Zacny 2005) included administration of acetaminophen alone, allowing for the comparison of the effects of hydrocodone/acetaminophen with acetaminophen alone. Thus, the study findings are likely due specifically to hydrocodone, as no measurable psychotropic effects were observed on any measure in the acetaminophen only condition. While the subjects in the study were recreational drug users, none had a history of abuse or dependence, according to DSM-IV criteria, although it is unclear if other psychiatric conditions or histories may have been present in the study sample.

Neuroimaging

Given the widespread use of opiates and the recent advances in neuroimaging techniques, it is surprising that so few studies have focused on the structural, spectroscopic and functional correlates of opiate use. Investigations have been limited by the inclusion of polydrug abusers as opposed to 'pure' opiate abusers, and small study samples. Structural imaging studies that use both computerized tomographic (CT) and magnetic resonance imaging (MRI) techniques have reported ventricular widening in opiate dependent subjects (Strang and Gurling 1989; Wiesbeck and Taeschner 1991) and reductions in frontal and temporal volumes (Lyoo et al. 2006), while others have not reported morphological abnormalities (Amass et al. 1992).

Data from animal studies are consistent with reports of structural alterations secondary to opioid use, as investigations have found neuronal size to be smaller in rats administered morphine compared to controls (Sklair-Tavron et al. 1996). In a seminal study, which utilized positron emission tomography (PET) techniques, London and colleagues examined the effects of morphine on glucose metabolism in 12 polydrug abusers (London et al. 1990). The authors found that whole brain glucose metabolism was decreased by 10% and that metabolism in telencephalic and cerebellar areas was decreased by 5–15%. After removing the possible confound of arterial blood gas from the cortical areas ($PaCO_2$ and PaO_2), decreased glucose metabolism remained in a number of cortical regions including the superior and middle frontal gyrus, the postcentral gyrus, the anterior cingulate gyrus, the paracentral lobule, and the gyrus rectus. Additionally, the investigators noted a left greater than right asymmetry in the temporal cortex. Interestingly, the study highlighted that the cerebral metabolic effects of morphine only paralleled the distribution of opioid receptors to a limited extent. Thalamic areas, which are rich in opiate receptors, did not demonstrate a significant change in glucose metabolism. Citing previous investigations which have demonstrated reduced glucose metabolism in human subjects following acute doses of benzodiazepines, barbiturates, amphetamines, and cocaine, the authors concluded that a reduction of cortical metabolism may be an important common element of the actions of drugs of abuse. Interestingly, it has also been reported that prior drug experience has an effect on glucose metabolism, suggesting that results from the London et al. study need to be considered in the context of previous drug use history.

Studies conducted using single emission computed tomography (SPECT) and PET techniques have revealed cerebral perfusion and metabolic abnormalities in opiate-dependent subjects (e.g., Christensen et al. 1996; Danos et al. 1998; Galynker et al. 2000; Kaufman et al. 1999; Krystal et al. 1995; Levin et al. 1995; London et al. 1989; Rose et al. 1996; Stapleton et al. 1995). These abnormalities may contribute to the behavioral and functional deficits found in this population. At present, few studies have examined the effects of treatment for opiate dependence on cerebral function. Galynker et al. (2000), using PET, reported a trend for improved cerebral metabolic rates in the anterior cingulate of methadone maintenance (MM) subjects (stabilized in treatment for 1.5 years) relative to subjects withdrawn from MM treatment. Magnetic resonance spectroscopy (MRS) has also been employed to examine neurochemical profiles of opiate-dependent individuals. Phosphorus magnetic resonance spectroscopy (^{31}P MRS) permits the quantification of high-energy phosphate compounds (e.g., phosphocreatine (PCr and nucleoside triphosphate (BNTP), which primarily reflects adenosine triphosphate (ATP) in brain); phospholipid metabolites

(membrane anabolites and catabolites) and inorganic phosphate (Pi). This imaging technique has been used to detect abnormal cerebral bioenergetic and phospholipid metabolism in cocaine- and opiate-dependent subjects (Christensen et al. 1996) and in opiate-dependent subjects examined after extended periods of MM (Christensen et al. 1996; Kaufman et al. 1999). The abnormalities included lower levels of PCr, which acts as buffer to maintain consistent levels of brain ATP, and elevated levels of phospholipid membrane precursors (phosphomonoesters) and break-down products (phosphodiesters). These alterations in cerebral bioenergetic status may reflect neuronal adaptation to the presence of opiates, but also may contribute to the cognitive deficits associated with opiate dependence. Cerebral metabolite profiles also differ from non drug-using cohorts during the initial weeks of methadone-maintenance treatment (Christensen et al. 1996; Kaufman et al. 1999; Silveri et al. 2004), the magnitude of which diminishes as a function of treatment duration (Christensen et al. 1996; Kaufman et al. 1999).

Forman et al. (2004) conducted a functional magnetic resonance imaging (fMRI) experiment in opiate dependent subjects on methadone maintenance, gender-matched healthy non-opiate using control subjects, and non-matched controls while they performed a go/no-go task. Compared with both control samples, opiate-addicted subjects demonstrated lower activity of the anterior cingulate cortex (ACC) and poorer task performance. Further, control subjects exhibited a relationship between activity within the ACC and false-alarm errors, which positively predicted task performance, a relationship that was not detected in the opiate addicted subjects. Results from this study suggest impaired cognitive control in the opiate addicted subjects, which may contribute to their inability to discontinue drug use. Potential limitations of this study include the exclusion of nicotine smokers from the control samples but not from the opiate dependent group, which may have affected the modulation of impulse control in opiate dependent subjects. Previous studies of smokers have demonstrated greater impulsivity in smokers relative to nonsmokers (Mitchell 1999; Bickel et al. 1999), which is similar to the pattern seen in opiate-dependent subjects (Petry et al. 1998). Further, since a subgroup of the opiate dependent subjects had not yet received their first dose of methadone, withdrawal effects cannot be ruled out entirely. Nevertheless, the pattern of altered cingulate activity during a task designed to measure impulsivity is consistent with other studies of opiate dependent subjects. In an fMRI study of heroin dependent patients and healthy controls, Lee et al. (2005) administered the Arrow task, a simpler version of the spatial congruence task with a go/no-go response pattern, while subjects completed scanning protocols. None of the patients was enrolled in a maintenance program, but they were admitted to a treatment center and had only taken heroin between three and seven hours prior to scanning. Heroin dependent patients made more errors than normal control subjects, and exhibited lower anterior cingulate and greater inferior parietal activation. These findings underscore the difficulty that opiate dependent subjects have with inhibition and impulsivity and complement neuropsychological data that suggest alterations in neural systems that mediate self-control and inhibitory processing.

Factors that Contribute to Addiction, Recovery, and Neuropsychological Performance

A number of factors have been shown to influence opioid addiction. These include, but are not limited to, age, age of onset of use, gender, prenatal exposure, race/ethnicity, level of education, employment status, geographic area, family history of drug abuse/dependence, poly-drug use, and criminal activity. These factors are important for understanding the development of addiction and are critical factors in interpreting neuropsychological test data. For instance, drug use and dependence are highly prevalent in the general population, as determined by the National Comorbidity Survey, which is a structured diagnostic interview administered to persons aged 15 to 54 years of age (Warner et al. 1995). This survey revealed that 51% of study participants have used at least one of the following substances: marijuana/hashish, cocaine/crack, heroin, hallucinogens, non-medical prescription psychotropic drugs such as sedatives, tranquilizers, stimulants, analgesics, or inhalants, in their lifetime, and 15.4% had used them in the past 12 months. Furthermore, 7.5% (14.7% of lifetime users) were dependent at some time in their lives and 1.8% were dependent within the past 12 months. When the age range was limited to 28–54 years of age, the prevalence of lifetime dependence was reduced to 5.3%, highlighting the relevance of age of onset of use in predicting substance dependence. Sex differences were also observed, with significantly more men reporting lifetime and 12-month use and dependence. This study demonstrates that factors such as age of first use, and existence and persistence of dependence are modifiable risk factors that must be examined at separate stages of the progression from use to dependence. These same factors are expected to be strongly associated with neuropsychological test performance.

Length of time between onset of abuse and dependence has been studied to provide a bridge between research on the addictive liability of drugs and on individuals' liability to addiction (Ridenour et al. 2005). The shortest length of time between onset of abuse and dependence was observed for cocaine and opiate use. Women and early initiators of

drug use also had a shorter length of time between onset of abuse and dependence than men and initiators that began their use later in life. No significant differences in length of time between onset of abuse and dependence were evident between African-American and Caucasian samples.

Substance abuse has been shown to run in families, with first-degree relatives of drug abusers typically displaying higher rates of substance abuse than relatives of non-drug users or the general population (Rounsaville et al. 1991). Furthermore, family history of substance abuse also influences drug abuse severity and treatment outcome (Pickens et al. 2001). Family-history-positive patients had more opioid dependence symptoms and were more likely to be classified as severely dependent when compared with family-history-negative counterparts. However, when enrolled in a methadone maintenance program, family-history-positive patients had lower rates of illicit opioid use but higher rates of cocaine use than family-history-negative patients. These effects remained significant after adjusting for gender and race. The results of this study suggest that family history, including both genetic and environmental factors, plays an important role in the susceptibility to heroin dependence and response to therapeutic methadone treatment.

Studies of psychiatric comorbidity in opioid abusers report that rates of comorbidity far exceed general population estimates. In a study by Brooner et al. (1997), psychiatric- and substance-use comorbidity was assessed in 716 opioid abusers seeking methadone maintenance, which revealed that the most common psychiatric diagnoses observed in 47% of the sample were antisocial personality disorder (25.1%), and major depression (15.8%). In addition, patients in this sample met the criteria for at least two substance use disorders, most often opioid and cocaine dependence, indicating the prevalence of polydrug use among opioid-using cohorts. Furthermore, demographic, substance-use history, and personality variables differentiated patients with comorbid psychiatric conditions from those without, and although no gender differences were observed, comorbid subjects were noted to have a more severe substance-use disorder. Rodriguez-Llera et al. (2006) examined young heroin users recruited from outside of the healthcare context. Of 149 individuals evaluated, 93% received a diagnosis of heroin dependence, 71% had cocaine dependence, and 32% of the subjects had never been treated for substance use. Two-thirds of the sample had lifetime psychiatric comorbidity, the most frequent conditions being antisocial personality (33%) and mood disorders (26%). A third of the sample was comprised of women; mood, anxiety, and eating disorders were the most common comorbid disorders in women compared to men. A substantial literature focuses on factors that significantly predict treatment response and recovery from opioid dependence. Marsh and colleagues (2005) have reported data from a single-site controlled trial comparing the efficacy of methadone, buprenorphine, and LAAM on the following outcome measures: (1) mean length of retention time in treatment; (2) percentage of urine samples positive for opioids during the maintenance phase; and (3) percentage of urine samples positive for cocaine during the maintenance phase. Factors significantly correlated with treatment outcome included marital status, employment status, poly-drug use, comorbid psychiatric illness, personality disorders, sex, and number of days paid in the 30 days prior to the study. More specifically, the combination of being both married and employed was associated with better treatment outcomes. Males also predicted better treatment outcome. Although patients with comorbid psychiatric conditions often demonstrate poorer treatment outcomes (McLellan et al. 1983, 1986), paradoxically, level of depression was significantly correlated with a positive treatment outcome. The authors concluded that therapeutic intervention focusing on mental health, in addition to drug abuse treatment, enhanced the investment of staying in treatment, particularly to have continued access to ancillary mental health treatment. Factors that were associated with negative treatment outcomes included a longer length of cocaine use and cocaine dependence, having an antisocial personality disorder or high levels of hostility, and the number of paid days in the 30 days prior to the study. The latter association was interpreted as greater income providing an increased opportunity for greater drug consumption. This measure of income was differentiated from employment, as the number of days paid presumably included both legal and illegal means of income. There also were nonsignificant trends for older age, number of years of education, and race (white) to be associated with better treatment outcomes, and number of months of alcohol abuse or dependence to be associated with poorer treatment outcomes.

Neural Mechanisms Associated with Opioid Abuse and Dependence

Opiate receptors are proteins embedded in the cell membrane to which morphine and other opiate agonists bind to initiate their pharmacological effects. The receptor subtypes that have been identified, mu, kappa, and delta, have been shown to have an affinity for experimental opioid compounds. Within the human brain, the highest concentration of opiate receptors has been identified in the limbic system, including the amygdala and hypothalamus, and in the medial portion of the thalamus and periaqueductal gray areas, which modulate emotional behavior, reward saliency, and pain perception. The high concentra-

tion of opiate receptors in the limbic system may underlie emotional changes induced by opiates, whereas sensory information about "slow pain" best relieved by opiate-based drugs is conveyed by the medial thalamus.

Alterations in neurotransmission and cellular activity associated with substance use have been characterized at various stages of the addiction cycle: acute exposure and reinforcement, chronic exposure, development of tolerance and sensitization, acute withdrawal, craving, and compulsive drug seeking and taking. There is little distinction made with regard to the neural underpinnings of substance abuse versus dependence. However, it is generally accepted that: (1) modification of neuronal systems occurs to counter acute drug effects, and persists once the drug is cleared (Koob et al. 1989); (2) neuroadaptation leads to the development of tolerance and dependence (Koob 1987; Trujillo 1995, 2000; Koob and Le Moal 2001); and (3) a rapid change from the active to the inactive drug state results in drug withdrawal (Cruz et al. 1996). Furthermore, it also has been established that drug-related stimuli, in the absence of drug exposure, has the ability to activate attentional and memory circuits that are associated with drug dependence and craving (Lubman et al. 2000). These findings suggest that direct pharmacological actions or exposure to drug-related stimuli acquire saliency through their temporal association with acute and chronic drug use (Sell et al. 1999).

Opioid abuse and dependence has been documented to alter several neural systems simultaneously, although common neurocircuitry elements have been identified in drug-seeking behavior regardless of drug type (see Koob 2003, Koob et al. 2004; Wise 1987, for review). There also is evidence that the neural circuitry of non-opiate users does not differ from opiate dependent individuals, but rather that the reward circuitry is activated to a greater degree in the latter group (Danglish et al. 2003). Neuronal alterations associated with chronic opioid use can be examined from the perspective of neural circuitry, neurotransmission, and basic cellular and molecular mechanisms. Neural networks that have been implicated in acute drug reward and the development of addiction generally include the nucleus accumbens, ventral tegmental area (VTA), prefrontal cortex (the anterior cingulate and the orbitofrontal cortices), amygdala, and hippocampus. Most notably, however, altered connectivity in the mesolimbic (which connects the VTA to the nucleus accumbens) and the mesocortical pathways (which connects the VTA to cortical areas in the anterior cingulate and orbitofrontal cortex) have been implicated in the compulsive drug seeking and taking that underlie addiction (Kalivas and Volkow 2005). At the levels of neurotransmitter systems, dopamine has been well established to play a role in the acute reinforcing effects of drug. Increases in mesolimbic dopamine release, down-regulation of dopamine D2 receptors, and increases in the firing rate of dopamine neurons in the VTA have been shown to contribute to the "hypofunction" of the dopaminergic system observed in addicted subjects (Volkow et al. 1996, 2004). Glutamate and GABA also play roles in compulsive drug seeking, diminished efficacy of non-drug stimuli to be rewarding (e.g., food), and reductions in response inhibition, or cognitive control (Guo et al. 2005; Laviolette et al. 2004; Kalivas and Volkow 2005). Additional cellular mechanisms and molecular elements also have been implicated in opioid dependence, including brain stress systems (e.g., corticotropin releasing factor, CRF) and transcription factors associated with acute drug effects and addiction (cyclic AMP, CREB, and Δ FosB) (Koob 2003; Nestler 1993; Nye and Nestler 1996). Taken together, neuronal and associated behavioral adaptations serve to increase the dose of the drug necessary to obtain rewarding properties and to increase the salience of drug-related stimuli, which together perpetuate the transition from acute drug use to chronic drug use to drug abuse and finally to drug addiction. These neuronal changes likely contribute to the observed decrease in inhibitory capacity seen in opiate users.

Summary

There are several variables that contribute to the development of opiate abuse and dependence, such as pharmacokinetic properties of the opiate self-administered and factors associated with an individual's vulnerability to develop an addiction. These factors may serve to mediate or moderate the manifestation and degree of cognitive impairments and alterations in brain structure and function observed in opiate-dependent populations (Fig. 1). In general, the use of opiates appears to have both acute and long-term effects on cognitive performance. In addition to the increased subjective effects reported by individuals who take opiates, the studies to date indicate a relatively broad spectrum of impairments in attention, concentration, visual and verbal recall, and visuospatial skills commonly associated with opioid administration. Reductions in psychomotor speed and reduced hand-eye coordination are also commonly reported. The long-term effects of opiate use appear to have the greatest impact on executive functions, including the ability to shift cognitive set, inhibit inappropriate response tendencies and in perseverative errors. In chronic opiate abusers, however, it is difficult to disentangle the effects of opiate use on cognitive performance from other factors that may affect neurobehavioral measures. For example, a number of early studies of chronic users included samples of poly-drug abusers, which may have confounded study results. Further, the areas of function most commonly

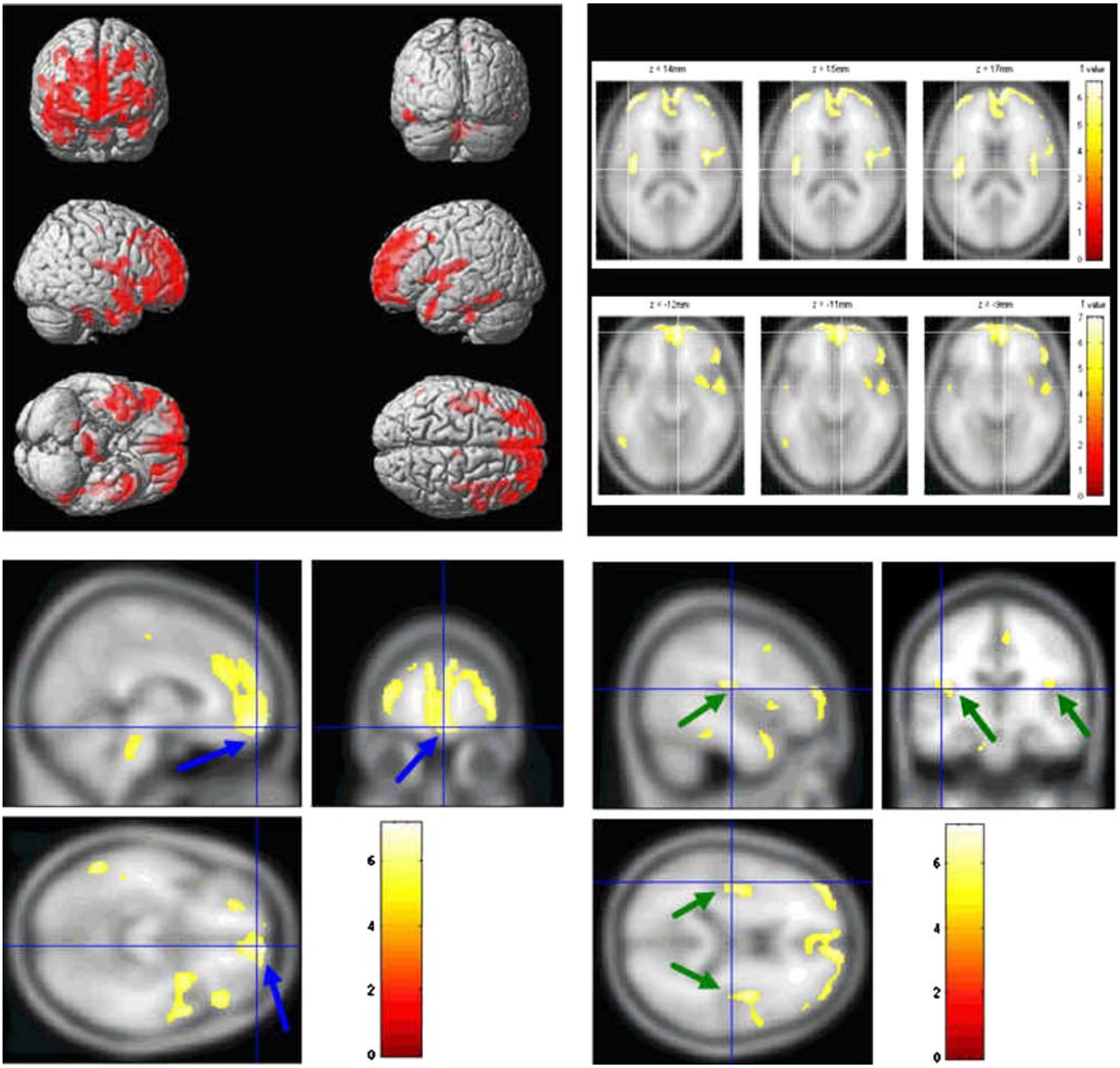

Fig. 1 Magnetic resonance images were acquired using a three-dimensional spoiled gradient echo pulse (SPGR) sequence in opiate dependent and healthy comparison subjects. Using voxel-based morphometry methods, the authors detected deficits in frontal and temporal gray matter regions in opiate users relative to healthy controls (Lyoo et al. 2006). Volume deficits in these regions are consistent with the neurocognitive changes reported in opiate dependent populations. From: Lyoo et al. (2006)

impaired in these subjects, specifically executive functions, are particularly sensitive to factors such as estimated levels of general intelligence or measures of IQ. As in most studies of substance abusers, finding a comparison population matched for IQ and other important demographic factors, including education, is challenging, and may make study interpretation difficult. This is further complicated by the difficulty in determining if, in fact, reductions in IQ often noted in substance abusers precede the drug use under study, or if IQ related measures are compromised secondary to drug use. Small sample sizes, common in investigations of substance abusing individuals, also reduce the generalizability of study findings.

Neuropsychology as a discipline can help characterize the effects of opiates on cognitive and emotional functioning, provide a description of the extent, scope, and quality of functioning, provide an estimate of baseline or premorbid level of functioning and provide a measure of an individual's potential and recovery course. While a single cross-sectional neuropsychological evaluation can offer a measure of an individual's overall cognitive strengths and weaknesses, repeated assessments over time provide an

index of change that allow factors such as age, education, treatment interventions, and disease state to be systematically evaluated. However, neuropsychological scores cannot be considered in isolation; important background variables, including handedness, cultural background, native language, education, socio-economic status, and generalized intelligence must be considered in the interpretation of all study results.

Additional neuropsychological studies of individuals with opioid abuse and dependence are needed to differentiate between neurocognitive deficits which may serve as predisposing risk factors for substance abuse, and deficits which are secondary to the acute or chronic use of opioids. These studies in combination with neuroimaging data will further clarify the impact of opioid use on neural systems, as well as aid in the development of treatment programs and strategies that promote recovery and reduce the risk of drug relapse.

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