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"Loss of Control" in Alcoholism and Drug Addiction: A Neuroscientific Interpretation

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Considerable neurological evidence indicates that the prefrontal cortex mediates complex "executive" functions including behavioral autonomy and self-control. Given that impairments of self-control are characteristic of alcoholism and other drug addictions, frontal lobe dysfunction may play a significant role in such compulsive behaviors. Consistent with this idea, recent research using brain imaging, neuropsychological testing, and other techniques has revealed that the frontal lobes are particularly vulnerable to the acute and chronic effects of addictive drugs, especially alcohol and cocaine. Evidence implicating a hyperdopaminergic mechanism of acute and chronic drug-induced frontal lobe dysfunction and interactions with premorbid factors and stress are discussed.

The notion that addictive disorders are characterized by a loss or impairment of self-control owes much to the work of alcoholism researcher E. M. Jellinek and has gained widespread acceptance. Jellinek (1952) originally defined *loss of control* in the context of alcoholism, such that the ingestion of a sufficient quantity of alcohol was said to induce a "chain reaction which is felt by the drinker as a physical demand for alcohol" (p. 679). Thus, by loss of control Jellinek meant a relative inability to stop drinking once drinking has started, resulting in a "bender," or binge-drinking episode. Later Jellinek (1960) also described the alcoholic's "inability to abstain" (p. 38) following a period of abstinence, another aspect of impaired control. A more recent application of the general concept of impaired control in addictions can be found in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., *DSM–IV;* American Psychiatric Association, 1994), in Substance Dependence criteria 3, "substance is often taken in larger amounts or over a longer period than was intended" and 4, "there is a persistent desire or unsuccessful efforts to cut down or control substance use" (p. 181). Loss of control in its broader sense thus encompasses both the relative inability of an alcoholic or drug addict to terminate consumption once initiated (often leading to bingeing to the point of incapacitation or exhaustion) and to refrain from substance use following a period of abstinence.

Loss of control was attributed by Jellinek to the pharmacological actions of alcohol on the nervous system following long-term heavy alcohol consumption by susceptible individuals. In his influential book *The Disease Concept of Alcoholism,* Jellinek (1960) theorized that loss of control reflects the desperate need of the "alcohol addict" to relieve aversive autonomic withdrawal symptoms. Jellinek thus interpreted alcoholism within the framework of the most popular addiction paradigm of his time, the opiate model, which equates addiction with physical dependence and the attendant need to take drugs for relief of withdrawal. However, much convergent evidence now indicates that self-medication of autonomic withdrawal symptoms is not the primary motive of most compulsive drug use (Jaffe, 1989; Lyvers, 1998; Widiger & Smith, 1994). Thus, if loss of control is indeed a real phenomenon with a pharmacological basis, as Jellinek assumed, then the question remains as to what is going on in the central nervous system (CNS) of addicts to induce it.

The pharmacological interpretation of loss of control has itself been criticized on a number of grounds. Critics have pointed out that alcoholics have demonstrated moderate drinking under certain incentive conditions or have otherwise failed to respond to alcohol ingestion in a manner consistent with the notion of an absolute, all-or-nothing loss of control in contrived laboratory situations (Marlatt, Demming, & Reid, 1973; Mello, 1983; also see review by W. R. Miller & Brown, 1991). For example, Marlatt et al. reported that alcohol consumption by men with alcohol problems was increased by instructions telling them that the beverage they drank contained alcohol but not by the actual alcohol content of the beverage they consumed, supporting an instructional set or expectancy interpretation of loss of control rather than a pharmacological interpretation. Subsequent studies have indicated, however, that actual alcohol ingestion does increase alcohol consumption independent of expectancy in severely dependent alcoholics (Ludwig, Bendfeldt, Wikler, & Cain, 1978; Stockwell, 1991; Stockwell, Hodgson, Rankin, & Taylor, 1982), supporting a pharmacological basis of loss of control in those with the most serious alcohol problems. Further, Maltzman (1994) questioned the relevance of Marlatt et al.'s findings to Jellinek's loss of control concept because Marlatt et al.'s participant sample may have consisted primarily of "problem drinkers" or "alcohol abusers" rather than Jellinek's truly alcohol-dependent "gamma alcoholics"; according to Jellinek (1960), only the latter group would be expected to exhibit loss of control in response to alcohol ingestion. Moreover, the results of at least two

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balanced placebo studies (L. J. Knight, Barbaree, & Boland, 1986; Korytnyk & Perkins, 1983) support a demand characteristics interpretation of so-called expectancy effects. In any case, reports that alcohol expectancy (or, alternatively, experimenter demand) can contribute to increased alcohol consumption certainly do not preclude the role of the well-established reinforcing actions of alcohol itself. Similarly, both alcohol expectancy and the pharmacological actions of alcohol have been reported to increase aggressive responses to provocation (Bushman, 1997; Bushman & Cooper, 1990; Hoaken, Giancola, & Pihl, 1998; Hull & Bond, 1986; Ito, Miller, & Pollock, 1996; Korytnyk & Perkins, 1983; Lang, Goeckner, Adesso, & Marlatt, 1975; Pihl & LeMarquand, 1998).

A more important point pertaining to criticisms of the loss-of-control concept is that most addicts appear to display a loss of control only intermittently; they are not absolutely out of control at all times and in all circumstances (Heather, Tebbutt, Mattick, & Zamir, 1993; Jellinek, 1960; N. S. Miller & Chappel, 1991). In other words, the loss of control in addiction is relative, not absolute (Glatt, 1983; Ludwig, Wikler, & Stark, 1974; Maltzman, 1994). A loose analogy can perhaps be drawn with the loss of control exhibited in another disorder characterized by compulsive behavior: obsessive–compulsive disorder (OCD). Ridley (1994) noted that in OCD "the behavior is voluntary in the sense that it can be suppressed for a very short time by 'will power' but it is also involuntary in the sense that the compulsive behavior invariably reappears after a short time" (p. 224). Further, like addicts' reports of an irresistable urge to use their drug ("craving"), the OCD patient "simultaneously expresses the view that they have an irresistable desire or need to perform (certain) actions while wishing that they didn't have to do them" (Ridley, 1994, p. 224). Another analogy is provided by Loewenstein (1996), who suggested that drug urges resemble other sporadically recurring "visceral" motivations such as hunger, thirst, or sleepiness, which vary on a continuum of intensity over time. Jellinek himself did not espouse a simplistic all-or-nothing interpretation of loss of control. For example, Jellinek (1960) wrote that "the loss of control does not emerge suddenly but rather progressively and . . . does not occur inevitably as often as the gamma alcoholic takes a drink" (p. 42). Descriptors such as *impaired control* (Edwards & Gross, 1976; Heather, 1991) and *dyscontrol* (W. R. Miller & Brown, 1991; Widiger & Smith, 1994) have recently been used as alternatives to loss of control in order to avoid the potentially misleading all-or-nothing implications of Jellinek's famous phrase.

Some critics of the loss-of-control concept have also pointed to evidence relating positive expectancies of drug effects to subsequent drug taking by addicts as consistent with a "pleasure-seeking" interpretation of addictive behavior (McAuliffe, Rohman, Feldman, & Launer, 1985; Mello, 1983). Indeed, the two drugs that today are considered most addictive—cocaine and heroin—are also widely believed to have exceptionally pleasureable effects, at least initially. However, the notion that addicts' compulsive drug use is due to their anticipation of pleasure seems incapable of accounting for tobacco dependence (Jarvis, 1994) as well as compulsive use of other drugs—including cocaine and heroin—when negative drug effects predominate (Lyvers, 1998; Robinson & Berridge, 1993). Moreover, recent studies of drug reinforcement in human drug abusers using doses of morphine or cocaine that were too low to elicit any subjective effects at all have indicated that a positive cognitive appraisal of drug effects is not necessary for drug self-administration rates to significantly exceed placebo (Fischman & Foltin, 1992; Lamb et al., 1991). Tiffany (1990) questioned whether any cognitive appraisal—including acknowledgement of subjective pleasure or even a "craving" state—is necessary for repetitive drug taking by addicts. He interpreted compulsive drug use as relatively "automatized" behavior driven largely by subcortical processes (also see N. S. Miller & Gold, 1994). Such considerations do not mean that the subjectively pleasurable consequences of drug taking are entirely irrelevant, but they suggest there is probably more to addictive behavior (in contradistinction to recreational drug use) than a simple search for pleasure.

Some of the more controversial critics of the notion that self-control is impaired in addicts have asserted that addiction phenomena such as compulsive drug-taking behavior, self-reports of loss of control, and relapse episodes are the behavioral expressions of false beliefs or expectancies derived from a pervasive "disease mentality," which erroneously attributes addicts' behaviors to chemicals rather than individual responsibility (Fingarette, 1988; Peele, 1987; Schaler, 1997). However, the idea that addictive behavior is simply a product of misguided thinking, a mere self-fulfilling prophecy, is contradicted by many reported cases where addicts, when they initiated drug use, had regarded themselves as immune to addiction, believed their drug of choice to be nonaddictive, or both. Many cocaine addicts in the 1970s and 1980s, for example, reported that they had never considered addiction a possibility when they initiated recreational cocaine use because they believed cocaine was a nonaddictive drug (Washton & Tatarsky, 1984). If cocaine addiction is simply the behavioral expression of expectations about cocaine, then these individuals—whose expectations were that cocaine is nonaddictive, consistent with the prevailing medical and popular wisdom of the time (see Akers, 1991; Grinspoon & Balakar, 1985; Van Dyck & Byck, 1982)—would never have called a cocaine hotline complaining of cocaine craving and a loss of control over cocaine use. The idea that addiction is a self-fulfilling prophecy also fails to explain the compulsive drug-taking behaviors exhibited by laboratory animals, which show some interesting parallels with the compulsive drug-taking and relapse patterns of human addicts (Stewart, 1983, 1984; Stewart, de Wit, & Eikelboom, 1984) and even loss of control (Wolffgramm & Heyne, 1995). On the basis of such evidence, as well as research on the neurophysiological mechanisms of drug reinforcement (see Di Chiara, 1995; Wise & Rompre, 1989), a number of biologically based theories of addiction have been offered in recent years (e.g., Koob & Le Moal, 1997; Modell, Mountz, & Beresford, 1990; Nesse & Berridge, 1997; Roberts & Koob, 1997; Robinson & Berridge, 1993; Stewart et al., 1984; Tiffany,

1990; R. A. Wise & Bozarth, 1987). The identification of underlying biological mechanisms in addiction does not render psychosocial factors irrelevant, but rather implies that such factors may interact in important ways with biology, as is widely acknowledged in the currently popular biopsychosocial perspective.

A Biological Basis for Loss of Control?

Given that a relative loss of control does appear to be a real phenomenon with a pharmacological component, the burden of proof falls on proponents of the loss-of-control concept to demonstrate some pharmacological action of a drug on the nervous system that could plausibly lead to impaired control over drug-taking behavior. Jellinek (1960) and Wikler (1980) are well-known for promoting the hypothesis that physical dependence is the basis of loss of control, but, as noted earlier, self-treatment of autonomic withdrawal symptoms cannot explain most compulsive drug use (Jaffe, 1989; Lyvers, 1998; Widiger & Smith, 1994). At best, the presence of withdrawal symptomatology can be regarded as a sign of chronic heavy use of depressant drugs and resulting neuroadaptation—a medically problematic consequence, but not primary cause, of such use. Recent biological theories of addiction have alternatively emphasized chronic drug-induced changes in brain dopamine systems as a possible basis of compulsive drug-taking (Kreek & Koob, 1998; Modell et al., 1990; Robinson & Berridge, 1993; Stewart et al., 1984; R. A. Wise & Bozarth, 1987; R. A. Wise & Rompre, 1989). Although convincing evidence of a causal link between changes in dopaminergic neurotransmission and addictive behavior is currently lacking, the present state of affairs probably reflects researchers' severely limited understanding of the immense complexities of brain–behavior relationships rather than an inherent problem with the concept of a drug-induced dysfunction of self-control processes per se.

One may also legitimately ask whether there is any evidence that self-control is ever present in the first place, much less the relative loss of it. In a recent review that addressed the issue of volition in the context of decision theory, Loewenstein (1996) pessimistically concluded that "at present ... there is little evidence beyond fallible introspection supporting ... complete volitional control of behavior" (p. 276). Indeed, the case for the folk psychology notion that most uncoerced human behavior is the result of deliberate choices seems to rest almost entirely on the verbal reports of individuals. On the basis of a subjective sense of freedom, most individuals verbally account for their own behavior in terms of decisions and choices. However, drug addicts often report that their behavior "feels" out of their control—they have tried to resist the tendency to drink or use drugs, but failed (Heather, 1991; Stockwell, 1991). Some critics might counter that addicts are at best mistaken and at worst lying when they say this. However, given that the only sources of data here are verbal reports of individuals, what reason do researchers have to believe only those individuals who claim they *have* control but not those who claim they have *lost* it in some respects? Verbal reports alone would seem to make the same sort of prima facie case for loss of control in addiction as they do for self-control in most everyday behavior of nonaddicts. What else is there to go on?

A different approach is to ask whether there are instances of brain damage that could be plausibly interpreted as reflecting a relative loss of self-control and that might thus conceivably offer some parallels with addictions. In fact, there appear to be a number of such cases. For example, split-brain patients often say that their left hand acts as if it has a mind of its own (Gazzaniga, 1970). In such patients, the left hemisphere, which mediates speech, no longer controls the left hand. Brain damage can thus render some aspects of behavior beyond the control of verbalizable processes. More pertinent to the general issue of self-control, however, are some of the tragic and fascinating behavioral consequences of frontal lobe damage. The frontal lobes, in addition to their motor functions, are thought to regulate the expression of a wide range of behaviors, apparently via prefrontal cortical inhibition of limbic and other cortical and subcortical structures (Arnsten, Steere, & Hunt, 1996; R. T. Knight, 1984; Le Moal & Simon, 1991; Masterman & Cummings, 1997; Starkstein & Robinson, 1997; Stuss, Gow, & Hetherington, 1992). According to Lhermitte (1986), normal frontal lobe functioning confers "personal autonomy" (p. 335), which he defined as the relative independence of the individual from the stimulus–response contingencies of the immediate environment. As demonstrated in Lhermitte's experiments with brain-damaged patients, lesions of the prefrontal cortex (the large portion of the frontal lobes anterior to the motor and premotor areas) can disrupt this autonomy to the extent that behavior becomes largely a function of external stimuli, an extreme form of disinhibition and loss of impulse control, which Lhermitte termed the *environmental dependency syndrome*. Aspects of autonomy such as self-control, delay of gratification, drive inhibition, and the anticipation of future consequences, as well as selective attention and certain kinds of abstract problem-solving, all seem to require the functional integrity of the "executive" prefrontal cortex (Berman & Weinberger, 1990; Bjorklund & Kipp, 1996; Brutkowski, 1964; Chao & Knight, 1995; Dias, Robbins, & Roberts, 1996; Goldman-Rakic, 1984; Luria, 1973; Malloy & Richardson, 1994; Sohlberg, Mateer, & Stuss, 1993; Stuss & Benson, 1984). Thus, a far-reaching but plausible interpretation of some of the more dramatic effects of prefrontal cortex damage asserts that volition is essentially a frontal lobe function (Norman & Shallice, 1986; Passingham, 1993; Ridley, 1994; Stuss & Benson, 1987; Wilkinson, 1991). A recent brain imaging study in normal volunteers lended support to this idea. Using positron emission tomography (PET), Frith, Friston, Liddle, and Frackowiak (1991) found that "willed actions" were specifically associated with activation of the prefrontal cortex, in contrast to "routine" or "automatic" tasks where the required response was specified by an external stimulus and did not activate the frontal lobes. Their finding is consistent with the views of Lhermitte, Luria, and others that neural circuits in posterior cortex and subcortical structures mediate programmed responses to stimuli, relatively "automatic" behaviors (Tif-

fany, 1990) or "fixed action patterns" (Ridley, 1994) that can be selectively modulated or inhibited by prefrontal cortical mechanisms, the latter giving behavior a certain flexibility and relative independence from the immediate stimulus environment. When the prefrontal cortex is damaged, this independence or autonomy may be lost to varying degrees, depending on the locus and extent of the lesion. Further, localized damage to distinct but linked subregions of the prefrontal cortex is accompanied by more specific effects that are assumed to reflect disruption of normal functioning of the parallel prefrontal-subcortical circuits associated with each area. Damage to the orbitofrontal area typically produces disinhibited behavior, perseveration, and failure to assess the consequences of one's actions; damage to the dorsolateral area results in cognitive deficits such as stimulus-boundedness and impairments of abstraction and set shifting; and damage to the medial prefrontal cortex–anterior cingulate is associated with apathy and deficits in future orientation (Kolb, 1977; Masterman & Cummings, 1997; Petry, Bickel, & Arnett, 1998).

The loss of autonomy evident in some patients with prefrontal lesions may not necessarily be verbalized as such by them. Profound denial and rationalization of behavioral deficits and gross abnormalities such as imitation behavior, utilization behavior, and environmental dependency often characterize such patients (Hoffman & Bill, 1992; Lhermitte, 1986; Lhermitte, Pillon, & Serdaru, 1986; Malloy, Bihrle, Duffy, & Cimino, 1993; Stuss & Benson, 1984). Denial and rationalization of abnormal or excessive behaviors are commonly observed in addicts as well. Yet, unlike the inappropriate behaviors consequent to frontal lobe damage, addictive behavior is also frequently accompanied by self-reports of a subjectively experienced loss of control—an admission, often following a period of denial, that there is indeed a problem of self-control. Why would denial (the refusal to acknowledge what would seem to be an obvious problem) be supplanted by verbalized recognition of a loss of control in addicts? A currently popular view of addiction is that compulsive drug-taking behavior is the manifestation of an "acquired drive," which, because of the direct actions of addictive drugs on motivational systems in the brain, shares some of the same brain circuitry implicated in natural drives—particularly the mesolimbocortical dopamine system that innervates areas such as the prefrontal cortex, nucleus accumbens and amygdala (Di Chiara, 1995; Gardner & Lowinson, 1993; Kreek & Koob, 1998; N. S. Miller & Chappel, 1991; N. S. Miller & Gold, 1993; Stewart et al., 1984; R. A. Wise & Bozarth, 1987; R. A. Wise & Rompre, 1989). From such a perspective, the drug-taking drive of addicts is no more phenomenologically chosen than are natural drives such as hunger, thirst or sleepiness. At least initially, an addict may not recognize that behaviors undertaken in response to the acquired drive are particularly inappropriate or abnormal. As the acquired drive gains in strength, addicts may attempt to maintain their excessive drug taking in the face of objections from others by using response strategies such as denial and rationalization. Only when the adverse consequences of the drug habit become too obvious to rationalize away or deny does the addict then try to resist or control behavioral tendencies linked to the acquired drive, and when such efforts repeatedly fail, the addict verbalizes a loss of control to account for the failed attempts at self-regulation (Orford, 1985). Patients with substantial frontal lobe lesions, on the other hand, may be less likely to express verbal awareness of their behavioral abnormalities because of a more profound impairment of self-monitoring than is typically present in addicts.

Intoxication and Frontal Brain Damage: Some Behavioral Parallels

Ridley (1994) distinguished relatively flexible, self-initiated or voluntary behaviors from the relatively inflexible fixed action patterns that are manifested as perseverative, stereotyped, or "stimulus bound" behaviors in various forms of psychopathology, including frontal lobe damage, addiction, OCD, schizophrenia, and autism. Ridley noted that there is clear evidence for frontal lobe dysfunction in OCD, schizophrenia, and autism; attention deficit hyperactivity disorder (ADHD) can now be added to this list as well (Arnsten et al., 1996). In the case of addiction, many of the behavioral changes induced by alcohol and other so-called addictive drugs seem loosely analogous to the disinhibition (Starkstein & Robinson, 1997) and environmental dependency (Lhermitte, 1986) exhibited by frontal lobe patients and may similarly reflect a diminution of inhibitory restraints normally mediated by the prefrontal cortex. For example, the acute behavioral effects of alcohol are often described or conceptualized in terms of disinhibition (Gorenstein & Newman, 1980; Hoaken, Giancola, & Pihl, 1998; Hull & Bond, 1986; Ito, Miller, & Pollock, 1996; Lau, Pihl, & Peterson, 1995; Maltzman & Marinkovic, 1996; Pihl & LeMarquand, 1998). Although some researchers have reported that alcohol expectancy can elicit an increase in disinhibited social behaviors such as aggressive responses to provocation irrespective of actual alcohol consumption (George & Marlatt, 1986; Hull & Bond, 1986; Lang et al., 1975), such disinhibition has also been shown to occur in response to alcohol intoxication irrespective of expectancy (Bushman, 1997; Bushman & Cooper, 1990; Hoaken, Giancola, & Pihl, 1998; Hull & Bond, 1986; Ito et al., 1996; Korytnyk & Perkins, 1983; Pihl & LeMarquand, 1998). Like frontal lobe patients, alcohol-intoxicated individuals often seem to lack normal awareness of their own errors, the impact of their behaviors on others, and the inappropriateness of certain behaviors, displaying a kind of failure of self-regulation (Peterson, Rothfleisch, Zelazo, & Pihl, 1990). Such effects may render alcohol use especially rewarding for highly "self-conscious" individuals (Hull, Young, & Jouriles, 1986). Another similarity between acutely alcohol-intoxicated individuals and frontal lobe patients is the "alcohol myopia" described by Josephs and Steele (1990), who noted that alcohol intoxication selectively impairs "controlled, effortful cognitive processing" while sparing "automatic" processing, and it "narrows attention to the most immediate internal and external cues" (p. 115). Yet another parallel concerns the profound dissociation between verbal and nonverbal behavior often manifest in frontal lobe

patients, such that the patients may verbally describe exactly what they are supposed to do in a given task situation, yet fail to implement the verbalized strategy, or even proceed to do just the opposite (Luria, 1964; Stuss & Benson, 1984; Stuss et al., 1992; Wilkinson, 1991)—a situation analogous to an addict's frequent broken promises to use moderately or abstain. A popular Japanese drinking game seems to take advantage of this frontal-lobe-like behavioral effect of alcohol. In the game, the winner of a trial of paper–scissors–rock commands "Look this way!" and points either up, down, right, or left; the opponent's task is to look any direction *other than* the one commanded. The penalty for losing is to down another drink. Of course, the higher the blood alcohol level the harder it becomes to resist the automatic tendency to visually follow the pointed finger, even though the task requirements are still easily verbalized. Such behavioral change resembles the "imitation behavior" of frontal lobe patients as described by Lhermitte et al. (1986) and is highly reminiscent of Luria's (1964) description of how frontal lobe patients consistently failed to perform even simple motor tasks in which they were required to do the opposite of what the examiner did.

Given the various apparent parallels described above, one may be tempted to ask whether there is any evidence that alcohol or other psychoactive drugs exert actions on the frontal lobes that might conceivably be the basis of drug-induced behavioral changes such as disinhibition and impaired self-control. In fact, recent evidence suggests that normal frontal lobe functioning may be particularly prone to disruption by a number of commonly abused psychoactive drugs, especially alcohol and cocaine.

Acute Effects of Alcohol on Indices of Frontal Lobe Functioning

Lyvers and Maltzman (1991a, 1991b) proposed that one of the acute CNS actions of alcohol in low to moderate doses is a relatively selective depression of frontal lobe activity, whereas high doses depress the cortex in a more nonselective fashion. As an indirect test of the first hypothesis, they used an electrodermal paradigm that yielded separate measures of signal-specific, novelty-induced, and nonspecific arousal. The transient increase in arousal evoked by a stimulus, or orienting reflex (OR), is a function of both stimulus novelty and stimulus significance. Stimuli that are meaningful or significant produce an enhancement of the OR above that produced by novelty alone. This enhancement of the OR by a signal is related to selective attention and appears to be regulated by the orbital subregion of prefrontal cortex (orbitofrontal cortex) according to animal studies (Skinner, 1988). In humans, damage to this area alters the signal OR and also typically produces disinhibited behavior and failure to adequately assess the consequences of behavior (Malloy et al., 1993; Malloy & Richardson, 1994; Masterman & Cummings, 1997; Starkstein & Robinson, 1997). Consistent with their hypothesis, Lyvers and Maltzman (1991a) found that a relatively low dose of alcohol in social drinkers (yielding peak blood alcohol levels of roughly .05%) caused selective changes in signal-specific skin conductance response–ORs (SCR-ORs) that resembled certain effects of frontal lobe damage on SCR-ORs as documented by Luria (1973) in human patients. Other effects of alcohol included significant increases in the frequency of spontaneous SCRs and the proportion of false alarms, both of which were consistent with a disinhibitory action of the drug.

Alcohol also selectively increased perseverative errors on the Wisconsin Card Sorting Test (WCST) without affecting nonperseverative errors (Lyvers & Maltzman, 1991b), resulting in higher percent perseverative error scores in intoxicated participants compared with controls. The perseveration measures of the WCST are often selectively elevated in patients with prefrontal cortex damage (Bornstein, 1986; Drewe, 1974; Heaton, 1981; Malloy & Richardson, 1994; Milner, 1964; Milner & Petrides, 1984; Stuss et al., 1983), hence the WCST has been rather optimistically called the "gold standard" among neuropsychological tests of frontal lobe dysfunction (Podell, Lovell, Zimmerman, & Goldberg, 1995), although significant differences in WCST performance between frontal- and nonfrontal-lesioned patients have not always been obtained (Anderson, Damasio, Jones, & Tranel, 1991). Recent cerebral blood flow, cerebral metabolic, and topographic EEG studies indicated that the prefrontal cortex is selectively activated during WCST performance in non-brain-damaged individuals, particularly the orbitofrontal and dorsolateral subregions (Berman et al., 1995; Nagahama et al., 1996; Rezai et al., 1993; Silberstein, Ciorciari, & Pipingas, 1995; Smith, Perdices, O'Sullivan, Large, & Barrett, 1997) and especially during set-shifting, consistent with the repeated failures to appropriately shift response sets, or perseveration, commonly observed in patients with prefrontal cortex damage. Further, WCST perseverative errors were negatively correlated with prefrontal cortical activation in a cerebral blood flow study of schizophrenics (Weinberger, Berman, & Zec, 1986). In a critical assessment of the utility of the WCST as an index of frontal lobe dysfunction, Mountain and Snow (1993) suggested that the seldom-used percent perseverative error score should best differentiate patients with frontal dysfunction from those with nonfrontal brain damage, as this measure controls for the correlation between perseverative errors and total errors (which includes nonperseverative errors). Although a neuropsychological test result by itself cannot be considered an unambiguous demonstration of a localized effect in the brain, Lyvers and Maltzman's finding that, in a large sample of social drinkers, a moderate dose of alcohol selectively increased all measures of perseveration on the WCST—including percent perseverative errors—is entirely consistent with their hypothesis that low to moderate alcohol doses produce a mild, temporary, and relatively selective disruption of frontal lobe functioning and implicates the dorsolateral and orbitofrontal subregions in particular.

Acute alcohol intoxication was also found to impair performance significantly on four other so-called frontal lobe tasks in a study by Peterson et al. (1990) using social drinkers. Although WCST performance was not affected in their study, Peterson et al. did not use the dual-run procedure

used by Lyvers and Maltzman (1991b), which is more sensitive to prefrontal cortex dysfunction than the standard WCST administration procedure (Stuss et al., 1983) and more selectively activates the prefrontal cortex than the standard procedure does, according to recent brain-imaging studies using PET (Berman et al., 1995; Smith et al., 1997). Interestingly, in contrast to the acute effects of alcohol itself, alcohol expectancy had no effect on psychophysiological and neuropsychological measures in the alcohol studies cited earlier, even though Lyvers and Maltzman's participants consistently reported that they definitely expected alcohol to impair their performance. Peterson, Finn, and Pihl (1992) subsequently found that a moderate dose of alcohol not only impaired performance of nonalcoholics on three presumed frontal lobe tasks, including the WCST, but in addition WCST errors were highly correlated with sober physiological reactivity to shocks and with the reactivity-dampening effects of alcohol in sons of male alcoholics, who are considered to be at an elevated risk for alcoholism. More recently, Hoaken, Assaad, and Pihl (1998) reported that a moderate dose of alcohol selectively impaired performance of social drinkers on several presumed frontal tasks but not nonfrontal tasks in a neuropsychological test battery. On the basis of the findings to date, performance of those neuropsychological tests considered to somewhat selectively tap cognitive functions and processes mediated by the prefrontal cortex appear to be particularly susceptible to the disruptive effects of low to moderate doses of alcohol in nonalcoholics.

In addition to the acute effects of alcohol on specific electrodermal and neuropsychological measures that are especially sensitive to changes in frontal lobe functioning—but can also be affected by changes elsewhere in the CNS—there is direct electrocortical evidence for an acute selective reduction of frontal activity following low to moderate alcohol doses in nonalcoholics (Lukas, Mendelson, Woods, Mello, & Teoh, 1989; Yamamoto & Saito, 1987). Further, de Wit, Metz, Wagner, and Cooper (1990) found that although low to moderate doses of alcohol produced global decreases in cortical metabolism as assessed by PET in nonalcoholics, the decrease in frontal cortical metabolism was especially pronounced. De Wit et al. noted that their results were seemingly at odds with cerebral blood flow studies that had found alcohol-induced increases in frontal lobe cerebral blood flow, but they attributed the latter findings to ethanol-induced vasodilation rather than metabolic changes in neurons (see also Tiihonen et al., 1994). Cerebral blood flow measures are highly sensitive to the vasoactive actions of drugs (London & Morgan, 1993; Mathew & Wilson, 1991), hence drug-induced changes in such measures should not automatically be interpreted as reflecting drug-induced changes in regional brain activity. A higher dose of alcohol was reported to depress cortical metabolism more nonspecifically in a PET study by Volkow et al. (1990), with the strongest effects in the occipital and prefrontal cortices in accordance with the cortical distribution of GABA-A receptors, where alcohol acts as an indirect agonist. Thus only low to moderate alcohol doses appear to have relatively selective effects on the frontal lobes, with high doses exerting a more nonspecific cortical depressant action that affects frontal and posterior regions similarly. Alcoholics, however, seem to be an exception to the latter generalization about high alcohol doses (see next section, Effects in Chronic Alcoholics). Nevertheless, even for lower doses the caveat should be added that as the whole cortex is affected by alcohol according to brain imaging studies, at least some behavioral effects of alcohol may be attributable to the drug's actions in nonfrontal cortical areas despite the fact that the frontal lobes appear to be most strongly affected.

Effects in Chronic Alcoholics

Volkow et al. (1990) also compared cortical metabolic responses to a high dose of alcohol in controls and detoxified alcoholics, and found that alcohol produced significantly greater depression of cortical metabolism in alcoholics than in controls in the prefrontal cortex but not other brain regions. Thus alcoholics appear to be more sensitive than nonalcoholics to the acute depressant actions of alcohol on the prefrontal cortex, a vulnerability that could be a consequence of chronic alcoholism or that may have predated alcohol use. Subsequent brain imaging research further revealed that chronic alcoholism was associated with abnormally low frontal cortical metabolism, with overall prefrontal and (more specifically) orbitofrontal metabolism gradually improving over a month of abstinence (Volkow et al., 1994). Although parietal cortical metabolism exhibited changes in the same direction, Volkow et al. noted that the "frontal cortex was the brain region that showed the largest increase in metabolism with detoxification and was the only region for which the relative measures were found to be significantly improved with detoxification" (pp. 181–182). Another recent PET study examined 30-day-plus abstinent alcoholics in two scans separated by intervals of from 10 to 32 months (Johnson-Greene et al., 1997). Alcoholics who had remained relatively abstinent between scans exhibited increases in glucose metabolism in the orbital and medial areas of the frontal lobes on the second scan compared with the first, whereas those who had relapsed between scans exhibited a decrease in metabolism in the same areas. The authors concluded that there is at least some degree of recovery from chronic alcohol-induced frontal lobe dysfunction following an extended period of abstinence. Decreased cerebral metabolism in the medial prefrontal cortex–anterior cingulate was also indicated in earlier brain-imaging studies of alcoholics (K. M. Adams et al., 1993; Gilman et al., 1990). Recent work by Volkow and her colleagues (see Gatley & Volkow, 1998) indicated persistent metabolic deficits in the anterior cingulate and orbitofrontal cortex in abstinent alcoholics assessed 6–8 weeks after detoxification.

Chronic alcoholism is often associated with signs of brain dysfunction or damage in which the frontal lobes (excluding motor cortex) tend to be most affected (Cala, 1987; Fleischhacker & Kryspin-Exner, 1986; Goldman, 1990; Harper & Kril, 1990; Harper, Kril, & Daly, 1987; Hunter et al., 1989; Joyce & Robbins, 1991; L. Miller, 1990; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Wilkinson, 1991). As a group, recovered alcoholic have sometimes been found to

exhibit enduring deficits on "frontal" tasks (Ciesielski, Waldorf, & Jung, 1995; Parsons & Farr, 1981), for example, generating excessive perseverative errors on the WCST (Beatty, Katzung, Moreland, & Nixon, 1995; Tarter, 1973). The degree of neuropsychological impairment has also been correlated with frontal hypometabolism as indexed by PET or cerebral blood flow in some recent studies (K. M. Adams et al., 1993; Gilman et al., 1990; Johnson-Greene et al., 1997; Moffoot et al., 1994) and with the likelihood of eventual relapse to alcoholism (see Goldman, 1990; Parsons, 1983; Yohman, Parsons, & Leber, 1985), although debate continues as to whether such apparent frontal lobe dysfunction primarily reflects the cumulative neurotoxic effects of alcohol, a premorbid condition, or possibly their interaction (Begleiter & Porjesz, 1995; Conrod, Peterson, & Pihl, 1997; Giancola, Martin, Tarter, Pelham, & Moss, 1996; Giancola, Moss, Martin, Kirisci, & Tarter, 1996; Giancola, Peterson, & Pihl, 1993; L. Miller, 1990; Peterson, Finn, & Pihl, 1992; Peterson & Pihl, 1990; Pihl & Peterson, 1995; Ryan & Butters, 1986; Tarter, Alterman, & Edwards, 1985; Tarter, Hegedus, Goldstein, Shelly, & Alterman, 1984; Tarter, Mezzich, Hsieh, & Parks, 1995; Tarter, Moss, & Vanyukov, 1995; Weinstein & Shaffer, 1993). In a review of brain-imaging studies of substance abusers, Volkow and Fowler (1992) concluded that "PET studies in patients with alcoholism have documented decreases in brain metabolism predominantly localized in the frontal cortex" (p. 264), and they noted that such abnormalities tend to outlast the withdrawal phase despite initial improvement. Quite plausibly, then, long-lasting frontal cortical changes resulting from chronic high alcohol intake may be at least partly responsible for the impairment of control exhibited by severely dependent alcoholics over their consumption of alcoholic beverages (which, as described previously, acutely depress prefrontal cortex activity), as well as some of the other behavioral and personality changes associated with chronic alcoholism (including denial, which Goldman partly attributed to impairment of cognitive self-monitoring functions normally mediated by the frontal lobes). The acute disruptive actions of alcohol on frontal lobe functioning are likely to be amplified in alcoholics, whose frontal lobes have already been compromised as a result of either chronic exposure to high alcohol concentrations or a premorbid condition that may have predisposed a subset of this group to alcoholism.

Regarding the latter alternative, a number of alcoholism researchers have recently presented a variety of evidence supporting the hypothesis that deficits in prefrontal and (in particular) orbitofrontal cortical serotonergic neurotransmission may underlie the impulsive and disinhibited personality traits, abnormally aggressive responses to provocation, impairments in executive functioning, and vulnerability to early onset alcoholism in a subset of persons with a family history of alcoholism or other substance abuse problems (Cloninger, 1987; Conrod et al., 1997; Heinz et al., 1998; Higley, Hasert, Suomi, & Linnoila, 1998; Higley & Linnoila, 1997; Higley, Suomi, & Linnoila, 1996; LeMarquand et al., 1998; Nielsen et al., 1998; Pihl & LeMarquand, 1998; Pihl et al., 1995; Virkkunen, Eggert, Rawlings, & Linnoila, 1996; Virkkunen, Goldman, Nielsen, & Linnoila, 1995; Virkkunen & Linnoila, 1997). An increased sensitivity to the dopaminergic or psychomotor stimulant actions of alcohol has also been indicated among nonalcoholic sons of male alcoholics (Pihl & Peterson, 1995), which is not incompatible with the previous hypothesis given the known interactions between serotonergic and dopaminergic systems (L. H. Parsons, Weiss, & Koob, 1996; Virkkunen et al., 1995). In laboratory animals, serotonergic lesion increases the rewarding effects of the dopamine reuptake blocker cocaine, and inhibition of serotonin release potentiates the rewarding effects of electrical stimulation of the mesolimbocortical dopamine system (see R. A. Wise, 1998); hence, a premorbid serotonergic deficit would appear to be quite consistent with an enhanced response to dopamine.

Neural Mechanisms of Acute and Chronic Alcohol Actions on the Frontal Lobes

The acute depressant action of low to moderate doses of alcohol on frontal cortical activity is probably mediated by alcohol's indirect agonist action at inhibitory GABA-A receptors and by its dopamine-releasing actions. Relatively low doses of alcohol are known to stimulate forebrain dopamine release in laboratory animals (Di Chiara & Imperato, 1985; Gessa, Muntoni, Collu, Vargiu, & Mereu, 1985; Wozniak, Pert, Mele, & Linnoila, 1991). Dopamine has a cortical distribution that is relatively concentrated in anterior regions, where it exerts inhibitory postsynaptic effects (Berger, Gaspar, & Verney, 1991; Bunney & Aghajanian, 1976; Glowinski, Tassin, & Thierry, 1984; Le Moal & Simon, 1991; Mora, Sweeney, Rolls, & Sanguinetti, 1976; Thierry, Mantz, Milla, & Glowinski, 1988). The prefrontal cortex in particular receives extensive dopaminergic innervation from subcortical dopamine systems (Berger et al., 1991; Le Moal & Simon, 1991; Volkow & Fowler, 1992), with dopamine especially concentrated in prefrontal cortical sites that support intracranial self-stimulation behavior (Routtenberg, 1981), the threshold of which is lowered by alcohol (Kornetsky & Porrino, 1992). Both excessive dopamine release and overstimulation of dopamine receptors in the prefrontal cortex have been shown to impair prefrontal-cortex-dependent cognitive functioning in laboratory animals (Arnsten & Goldman-Rakic, 1998; Murphy, Arnsten, Jentsch, & Roth, 1996; Zahrt, Taylor, Mathew, & Arnsten, 1997). The inhibitory postsynaptic effects of alcohol-induced dopamine release in the prefrontal cortex, as well as inhibition arising from alcohol's potentiating action at cortical GABA-A receptors (which have a widespread cortical distribution), are thus probably sufficient to explain the acute depressant action of alcohol on the frontal lobes as well as alcohol-induced impairments on cognitive tasks that more or less specifically tap functions mediated by the prefrontal cortex.

According to Modell and his colleagues (Modell et al., 1990; Modell & Mountz, 1995; Modell, Mountz, Glaser, & Lee, 1993), chronic high alcohol intake (with repeated stimulation of dopamine release by alcohol) eventually leads to depletion of dopamine stores, resulting in supersensitivity of postsynaptic dopamine receptors and an increased dopa-

minergic response to alcohol manifested in alcoholics as craving and loss of control. Supporting this hypothesis, Modell et al. (1993) reported that dopamine-blocking drugs inhibited alcohol-induced craving and reduced alcohol consumption in alcoholics. Thus, alcoholism may fit with currently popular biological theories of addiction that were originally based on the dopaminergic actions of psychostimulants and opioids (e.g., Robinson & Berridge, 1993; Stewart et al., 1984; R. A. Wise & Bozarth, 1987) and that emphasize chronic drug-induced sensitization in the mesolimbocortical dopamine system as a neurophysiological basis of addictive behavior. However, a crucial detail of Modell et al.'s theory appears to be incorrect in light of recent work by Linnoila and his colleagues (Hommer et al., 1997). Modell et al. proposed that sensitization of the dopaminergic orbitofrontal–basal ganglia–thalamocortical circuit as a result of chronic alcoholism eventuates in hyperactivity of the orbitofrontal cortex associated with a pathological craving state, especially when alcohol is consumed. Hommer et al. found that the drug m-chlorophenylpiperazine (mCPP), which acts at serotonergic receptors, significantly activated the orbitofrontal cortex, prefrontal cortex, and subcortical components of the basal ganglia–thalamocortical dopamine circuit as measured by PET in nonalcoholic controls, but failed to activate the orbitofrontal cortex and other frontal areas in detoxified chronic alcoholics, and it activated the basal ganglia and thalamus to a much lesser degree than in controls despite the fact that other brain regions were similarly activated in both groups. The frontal lobes were described as particularly unresponsive in alcoholics compared with controls, and the authors related this to the signs of mild cognitive dysfunction and alexithymia that are commonly observed in alcoholic participants. Hommer et al. interpreted their results as reflecting hypoactivity of the orbitofrontal cortex, prefrontal cortex, basal ganglia and thalamus in chronic alcoholism, in contradistinction to the hyperactivity of these same areas predicted by Modell et al. Moreover, the brain-imaging studies discussed above clearly indicate that alcohol acutely depresses prefrontal and orbitofrontal activity in alcoholics, again contrary to Modell et al.'s model, which specified an excitatory response of these brain regions to alcohol associated with induction of craving. Hommer et al. tentatively attributed the hypoactivity of these brain regions in alcoholics to deficient excitatory serotonergic neurotransmission, but abnormally elevated inhibitory dopaminergic neurotransmission (perhaps involving supersensitive postsynaptic dopamine receptors) would be expected to produce similar effects on regional brain activity in those same areas. Pihl and LeMarquand (1998) suggested that one of the effects of chronic alcoholism is a reduction in serotonergic functioning in the prefrontal cortex, leading to an increased likelihood of disinhibited and impulsive behaviors, including aggression and excessive alcohol intake. Of course, chronic alcohol-induced changes in inhibitory dopaminergic and excitatory serotonergic neurotransmission might both contribute to such impairments of frontal lobe mediated behavioral self-regulation. An interaction between these neurotransmitter systems—specifically, excessive dopaminergic neurotransmission coupled with insufficient serotonergic activity—has been implicated in OCD (McDougle, Goodman, Delgado, & Price, 1989).

Acute enhancement of dopaminergic neurotransmission in the forebrain is an effect common to all so-called addictive drugs, including cocaine, amphetamine, opiates, and nicotine (Di Chiara, 1995; Koob & Bloom, 1988; Miller & Gold, 1993; Stewart et al., 1984; Vezina, Blanc, Glowinski, & Tassin, 1992; R. A. Wise & Rompre, 1989). Do these drugs also have relatively selective and behaviorally significant effects on prefrontal cortex functioning? A variety of evidence suggests that at least some of them do. In a recent study comparing the general behavioral effects of reinforcing versus nonreinforcing drugs in rats, Loh, Smith, and Roberts (1993) reported that heroin, amphetamine, and nicotine all induced perseveration (defined by a reduction of normal variability in the pattern of maze exploration), whereas nonreinforcing psychoactive drugs such as scopolamine and haloperidol did not have this effect on behavior. As perseveration in laboratory animals as well as humans has been associated with prefrontal lesions (Hotz & Helm-Estabrooks, 1995; Mishkin, 1964; Stuss & Benson, 1984), especially in areas receiving strong dopaminergic projections (Le Moal & Simon, 1991; Sandson & Albert, 1987), the perseveration induced by heroin, amphetamine, and nicotine is consistent with drug-induced disruption of normal prefrontal cortex functioning. However, current evidence for a behaviorally significant frontal lobe action of addictive drugs other than alcohol is most convincing for cocaine.

Acute Effects of Cocaine on Indices of Frontal Lobe Functioning

Many of the acute behavioral effects of cocaine (as well as the somewhat similar psychomotor stimulant amphetamine) in humans seem consistent with depression of certain prefrontal-cortex-dependent functions. Cocaine reliably produces "ego inflation" and disinhibited social and sexual behavior (Gold & Verebey, 1984; Washton & Gold, 1984), and cocaine- or amphetamine-induced increases in stimulus manipulation and stereotypy (Ridley, 1994) seem analogous to the spontaneous utilization behavior (Shallice, Burgess, Schon, & Baxter, 1989) and perseverative tendencies, respectively, of frontal lobe patients. The prefrontal cortex is a significant site of cocaine reinforcement in laboratory animals (Goeders & Smith, 1985). Prefrontal lesions induce stereotypy and perseveration in laboratory animals and potentiate psychomotor stimulant effects by removing the inhibitory influence of the frontal lobes on subcortical dopamine systems (Le Moal & Simon, 1991; Ridley, 1994). Prefrontal lesions involving dopaminergic terminals also produce behavioral "supersensitivity" to the reinforcing actions of cocaine in rats (Schenk, Horger, Peltier, & Shelton, 1991), probably due to up-regulation of postsynaptic dopamine receptors. In intact animals, the prefrontal cortex is the cortical region that is most sensitive to cocaine, showing metabolic changes before other areas following low cocaine doses (Porrino, Domer, Crane, & Sokoloff, 1988).

Brain imaging studies of human cocaine abusers by

London and her colleagues (Herning, Glover, Koeppl, Phillips, & London, 1994; London, 1989; London & Morgan, 1993), using PET and topographic electroencephalogram (EEG), have revealed that acute cocaine intoxication is associated with globally decreased glucose utilization and increased EEG beta power in the cortex, with relatively greater effects in frontal areas; glucose utilization was also decreased in the basal ganglia, another area receiving substantial dopaminergic innervation. London et al. (1996) attributed the cocaine-induced decreases in cortical metabolism, as revealed by PET, to cocaine's acute enhancement of dopaminergic neurotransmission. These results parallel the acute effects of cocaine on cerebral glucose utilization in nonhuman primates, where cocaine-induced decreases in prefrontal and orbitofrontal metabolism were observed as well as decreases in several subcortical areas including the nucleus accumbens and anterior thalamus (Lyons, Friedman, Nader, & Porrino, 1996). However, as in the brain-imaging studies of alcohol intoxication described earlier, the cocaine-induced decrease in cerebral metabolism affected the entire cortex in humans and was not restricted to the frontal lobes, though the latter appeared to be most strongly affected.

In another human brain-imaging study, acute cocaine-induced decreases in frontal lobe cerebral blood flow were significantly correlated with increases in self-reported cocaine "high" (Pearlson et al., 1993). Similar localized effects of acute cocaine on cerebral blood flow as measured by single photon emission computerized tomography (SPECT) were subsequently reported by Wallace et al. (1994). On the basis of the anterior localization of such effects, Kosten, Malison, and Wallace (1996) attributed these localized cocaine-induced changes in cerebral blood flow to cocaine's action at dopaminergic terminals, as the vasoconstricting action of cocaine would be expected to produce more widespread changes in the cortex. In contrast to the effects of cocaine, PET studies of another psychomotor stimulant, amphetamine, indicated that this drug nonselectively reduced whole cortical metabolism in both schizophrenics and controls (Wolkin et al., 1987) but produced selective changes in frontal areas in participants with ADHD (Matochik et al., 1993). Wolkin et al. suggested that the unexpected nonselective cortical effects they observed may be attributable to amphetamine's potent norepinephrine-releasing action, as that neurotransmitter has a more diffuse distribution in the cortex than dopamine, which is relatively concentrated in anterior regions (Arnsten & Goldman-Rakic, 1984; Berger et al., 1991; Bunney & Aghajanian, 1976). Compared with amphetamine, the actions of cocaine include relatively greater enhancement of dopaminergic and relatively weaker enhancement of noradrenergic neurotransmission. However, the reinforcing actions of both amphetamine and cocaine appear to be dopamine-dependent (see Di Chiara, 1995), and chronic amphetamine treatment in rats was recently found to induce long-term structural changes in prefrontal cortex and nucleus accumbens neurons that were likely targets of inhibitory dopaminergic innervation (Robinson & Kolb, 1997).

Cocaine Addiction and the Prefrontal Cortex

In PET studies of cocaine addicts undergoing detoxification, early cocaine abstinence was associated with increased metabolic activity in the orbitofrontal cortex and basal ganglia (Volkow, Fowler, Wolf, et al., 1991), an effect interpreted as reflecting decreased brain dopamine activity during acute (<72 hr) cocaine withdrawal. Volkow et al. (1992) subsequently reported that cocaine addicts in treatment who were tested up to 6 weeks after last cocaine use showed selectively decreased frontal cortical metabolism compared with nonaddict controls, a difference that was characterized as "marked." After 3 months of abstinence, addicts continued to show selectively decreased frontal cortical metabolism compared with controls, and the magnitude of the decrease was correlated with severity of previous cocaine use assessed in terms of self-reported average weekly dose and number of years of cocaine use. Patients with concurrent psychiatric diagnoses or problems with other substances had been excluded from the study, leading Volkow et al. to tentatively attribute the frontal cortical changes to enduring effects of heavy cocaine use rather than premorbid pathology. Volkow et al. (1993) later reported that long-term abstinent cocaine addicts displayed persistent reductions in prefrontal–orbitofrontal cortical metabolism compared with nonaddicts. The magnitude of these reductions was significantly related to reduced D2 dopamine receptor availability in prefrontal–orbitofrontal cortex, a relationship that suggests persistent down-regulation of inhibitory postsynaptic dopamine receptors in response to chronically heightened dopaminergic activity. Although cocaine blocks reuptake of serotonin in addition to dopamine, cocaine abusers do not appear to differ from controls in terms of the availability of 5-HT2 receptors (see Gatley & Volkow, 1998; Kreek & Koob, 1998). Volkow et al. proposed that the reduced activity of frontal lobe structures observed in cocaine addicts reflected a chronic cocaine-induced dysfunction or sensitization of the mesocortical dopamine system and may account for the relative inability of addicts to refrain from cocaine use when confronted with cocaine-related cues. In recent reviews of these and other studies, London and her colleagues (Bolla, Cadet, & London, 1998; London et al., 1996) concluded that subtle deficits in executive functioning in cocaine addicts are related to dysfunction of specific areas of the prefrontal cortex as indicated in brain imaging studies, especially the orbitofrontal cortex and anterior cingulate. Bolla et al. argued that these problems most likely reflect effects of heavy cocaine use rather than premorbid pathology.

In another recent PET study, cocaine craving was significantly correlated with the degree of mu opioid receptor binding in the frontal cortex of cocaine addicts during the first few days of cocaine abstinence (Zubieta et al., 1996), and anterior cortical mu receptor binding was significantly elevated compared with nonaddict controls across 4 weeks of abstinence. Zubieta et al. suggested that the apparent up-regulation of mu opioid receptors during cocaine abstinence reflected interactions between endogenous opioid and dopamine systems and may account for the suppression of

cocaine craving by the partial mu agonist buprenorphine in recent clinical trials. Alternatively, the elevated frontal cortical mu receptor binding in addicts may have predated their initiation of drug use and could be related to a predisposition to drug abuse rather than a chronic effect of cocaine.

"Hypofrontality" in Cocaine Addicts: Premorbid Pathology or Effect of Chronic Cocaine Abuse?

Majewska (1996) noted that "hypofrontality" is common to chronic cocaine abusers, individuals diagnosed with ADHD, and patients with frontal lesions. She related this to a number of behavioral abnormalities common to all three conditions, including disinhibition, impulsivity, and cognitive and attentional deficits. Bauer (1996) described persistent attentional deficits in abstinent cocaine addicts. Further, compared with controls or abstinent alcoholics, abstinent cocaine addicts displayed significantly smaller P300 responses (an electrocortical correlate of attention) to signal stimuli, but not novel nonsignal stimuli, for up to 3 months after the last use of cocaine; the effect was most pronounced at frontal electrode sites. Bauer noted that these deficits were unrelated to premorbid factors and hence were tentatively interpreted as neurotoxic sequelae of cocaine addiction. On the other hand, Herning and King (1996) argued that their similar electrocortical findings were unrelated to self-reported intensity of cocaine use and therefore may have reflected premorbid factors known to be associated with both reduced P300 and increased susceptibility to substance abuse, including ADHD, family history of alcoholism, and antisocial personality traits (see Begleiter & Porjesz, 1995; Brigham, Herning, & Moss, 1995). Herning and King also observed increased EEG beta activity in 9-day abstinent cocaine addicts compared with nonaddict controls, and at frontal sites only, EEG beta was significantly correlated with the number of grams of cocaine used in the week prior to abstinence. They noted that the EEG and other electrocortical changes observed in cocaine addicts were unrelated to the dysphoria of acute abstinence, and they suggested that such changes may instead be related to cocaine craving and the enduring tendency to relapse. Herning and King tentatively interpreted the increased EEG beta in addicts as reflecting cocaine-induced neuron loss. They suggested that cocaine craving results from reduced cortical inhibition of subcortical systems concerned with incentive motivation.

Kosten et al. (1996) proposed that neuron loss due to chronic cocaine abuse may have a vascular basis. They noted that the chronic cortical perfusion deficits observed in abstinent cocaine addicts are enhanced by acute cocaine, which probably exacerbates the chronic condition. Volkow, Mullani, Gould, Adler, and Krajewski (1988) invoked vascular pathology and chronic changes in prefrontal cortex dopamine terminals to explain the reductions in prefrontal cortical cerebral blood flow they observed with PET in detoxifying cocaine addicts at 3 and 10 days post-cocaine. Tumeh, Nagel, English, Moore, and Holman (1990, 1991) described focal perfusion deficits, revealed by SPECT, as most common in the frontal and temporal lobes of cocaine abusers. Buprenorphine treatment only partially improved the enduring cortical perfusion deficits revealed by SPECT in abstinent cocaine addicts in a study by Holman et al. (1993), who tentatively attributed such deficits to long-term vascular effects of cocaine. In recent work by Woods et al. (described in Kosten et al., 1996), deficits in cerebral blood flow were especially pronounced in the frontal and parietal cortices of patients who were dependent on both cocaine and alcohol, suggesting a possible synergistic action of the two drugs on this brain-imaging variable.

In their SPECT study of detoxifying cocaine addicts, Kosten et al. (1996) described how the density of striatal dopamine transporters was substantially elevated during initial cocaine abstinence, but normalized over 2–4 weeks. The time course of normalization of dopamine transporter densities in the striatum roughly parallelled the time course of normalization of depression and other negative affective disturbances during cocaine withdrawal as reported in clinical work. In contrast to Kosten et al.'s findings for the striatum, Hitri, Casanova, Kleinman, and Wyatt (1994) reported that human cocaine abusers showed a significant loss (38%) of available dopamine transporter receptors in the prefrontal cortex compared with nonusers on postmortem examination, implying that chronic cocaine-induced changes in prefrontal cortical neurons may accompany the development of cocaine dependence. The effect was unrelated to the use of other drugs, including alcohol, and physiological levels of cocaine were too low for the effect to be attributable to acute occupation of dopamine transporters by the drug. A post-cocaine reduction in prefrontal cortex (but not striatal) dopamine transporters was found to persist up to 12 weeks after the last cocaine dose in rats (Hitri & Wyatt, 1993), a result the authors attributed to a neurotoxic effect of chronic cocaine on the frontal lobes. Intriguingly, other recent work has indicated that dopamine itself can be neurotoxic to cortical neurons (Alagarsamy, Phillips, Pappas, & Johnson, 1997).

O'Malley and Gawin (1990) reported that recently abstinent "pure" cocaine addicts—whose substance problem was restricted to cocaine alone—were significantly impaired compared with controls on the Halstead–Reitan Battery's Category Test, an index of abstracting ability and cognitive flexibility that is thought to be less specifically sensitive to prefrontal cortex functioning than the WCST (Malloy & Richardson, 1994; Stuss & Benson, 1984; but see Johnson-Greene et al., 1997). By contrast, a sample of long-term abstinent cocaine addicts performed no differently from controls on the Category Test, suggesting that the impairment observed in recently abstinent addicts was reversible. Relatively persistent cocaine-induced functional changes in the prefrontal cortex were suggested in a recent study by Beatty et al. (1995), who found that 3–5 week abstinent cocaine addicts displayed significantly more perseveration than nonaddict controls on the WCST, with no differences on other WCST performance measures. Beatty et al. tentatively ruled out premorbid factors such as residual ADHD as explanations for the observed neuropsychological deficits in their inpatient treatment sample of relatively "pure" long-term cocaine addicts. More recently, chronic amphetamine

abusers and patients with orbitofrontal lesions exhibited comparable deficits on a decision-making task (Rogers et al., 1999). The degree of deficit was correlated with years of amphetamine abuse, suggesting a causal role of the psychostimulant drug. On the other hand, measures of impulsivity—defined as a lack of behavioral self-control and an inability to delay gratification—were highly correlated with subjective cocaine "high" in a study of cocaine users by Cascella et al. (1994), suggesting that a preexisting frontal lobe deficit manifested as impulsive personality traits might uniquely predispose a subset of cocaine users to exaggerrated cocaine euphoria and subsequent addiction. Impulsivity and card-sorting test perseveration were also recently reported to be significantly correlated in non-addicts (Van den Broek & Bradshaw, 1993).

Chronic abusers of both cocaine and heroin showed less frontal lobe white matter volume than non-substance-abusing controls in a recent magnetic resonance imaging (MRI) study by Schlaepfer, Noss, Soria-Heidbreder, and Pearlson (1996). This difference could conceivably be due to one or both drugs, or (again) it may reflect a preexisting condition that predisposed participants to drug abuse. Liu, Matochik, Cadet, and London (1998) also recently reported that 2-week abstinent polysubstance abusers—most of whom preferentially abused cocaine—exhibited smaller prefrontal cortex volumes compared with controls on the MRI, but in their study the difference was specific to gray matter, paralleling similar MRI findings reported by Pfefferbaum et al. (1997) in alcoholics. The number of years of cocaine abuse was significantly negatively correlated with prefrontal cortex volume. Liu et al. argued that although their results could reflect pre-drug prefrontal pathology in the drug abuser sample (despite an absence of comorbid psychiatric disorders), a more likely interpretation is that chronic drug abuse caused prefrontal cortex damage. Other recent work has found signs of cerebral atrophy and lesions in the frontal lobes of chronic cocaine abusers, which are generally interpreted as effects of chronic cocaine exposure rather than premorbid conditions (Brown, Prager, Lee, & Ramsey, 1992; Majewska, 1996; Pascual-Leone, Dhuna, & Anderson, 1991), but the basic issue of whether the observed frontal deficits primarily reflect pre-drug pathology or an effect of chronic cocaine abuse remains unresolved. Both types of processes may be important in cocaine addiction, as increasingly appears to be the case in alcoholism (as discussed previously). However, Bolla et al. (1998) recently argued that heavy cocaine abuse leads to deficits in executive functioning due to cocaine-induced damage to prefrontal brain regions, particularly the orbitofrontal area and anterior cingulate. They suggested that such cocaine-induced deficits help perpetuate addiction by rendering the addict less able to engage in self-monitoring and behavior change.

Interactions between the dopamine system and the frontal lobes were emphasized in a recent theory of cocaine addiction offered by Volkow, Ding, Fowler, and Wang (1996). Volkow et al. postulated that chronic cocaine-induced dysfunction of the orbitofrontal cortex underlies cocaine addicts' loss of control and craving when they are exposed to cocaine or cocaine-related cues. Interestingly, Insel (1992) described a case where localized damage to the orbitofrontal cortex apparently triggerred severe OCD symptoms in a previously non-OCD individual, paralleling results from animal studies conducted by Kolb (1977), who described the emergence of perseverative, stereotyped, and hyperactive behavior following lesions of the orbitofrontal cortex. In cocaine addiction, according to Volkow et al., dopaminergic neurotransmission in the orbitofrontal cortex has become hyperresponsive to cocaine and cocaine-related cues, such that stimulation of dopaminergic neurotransmission by cocaine (or by the sight of cocaine paraphernalia or other such conditioned stimuli) triggers dopamine release and promotes compulsive drug taking even when subjectively pleasureable effects of cocaine no longer reliably occur. Volkow et al. thus suggested that there is a progressive loss of normal frontal-lobe-mediated inhibitory regulation of stimulus-specific consummatory behavior in cocaine addicts, manifested as a relative loss of control (or impairment of control) that is more or less independent of any pleasureable consequences of cocaine ingestion once a pattern of compulsive use has developed. Further, paralelling Modell et al.'s theory of alcoholism, the enduring changes in dopamine circuits innervating the orbitofrontal cortex are assumed to render postaddicts highly susceptible to craving and readdiction whenever they are exposed to cocaine-related cues or (especially) cocaine itself, accounting for relapses to addiction even long after detoxification (Jaffe, Cascella, Kumor, & Sherer, 1989; O'Brien, Childress, McLellan, & Ehrman, 1992). However, like Modell et al., Volkow et al. postulated that the obsessive craving state induced by chronic abuse of drugs that enhance dopaminergic neurotransmission is associated with hyperactivity of the orbitofrontal cortex, whereas in their own and other studies cited earlier, acute intoxication with cocaine or alcohol (which triggers the most intense craving in cocaine addicts and alcoholics, according to the theories) was associated with *depression* of prefrontal–orbitofrontal activity, consistent with the hyperdopaminergic state acutely induced by those drugs. Hyperactivity of the orbitofrontal region was observed only during acute cocaine abstinence and was interpreted as reflecting a *hypo*dopaminergic withdrawal state. Thus, Volkow et al.'s hypothesis linking orbitofrontal hyperactivity to drug urges is—like the alcoholism model of Modell et al.—inconsistent with the well-established, dopamine-dependent "priming effect" of drugs such as alcohol, cocaine, or heroin, in which acute drug intoxication reinstates drug-reinforced responding (de Wit, 1996; Stewart, 1984) and which Stewart proposed as a likely mechanism of loss of control. The orbitofrontal hyperactivity observed by Volkow et al. during acute cocaine withdrawal is instead consistent with an acute *reduction* in mesocortical dopaminergic neurotransmission and may be accompanied by anxiogenic mentation possibly including conscious efforts to ward off feelings of craving (Volkow, Fowler, Wolf, et al., 1991). However, Volkow et al. (1999) recently reported that the intensity of self-reported cocaine craving was positively correlated with right-hemisphere orbitofrontal and striatal metabolism in cocaine addicts given the psychostimulant

methylphenidate (which had variable effects on cerebral metabolism), partially supporting their hypothesized link between heightened orbitofrontal activity and cocaine craving. In any case, addicts' self-reports of craving appear to be poorly related to drug-taking behavior according to recent work (N. S. Miller & Gold, 1994; Tiffany, 1990; Weiss, Griffin, & Hufford, 1995; S. P. Wiseman & McMillan, 1995); hence, the relevance of self-reported craving to the impairment of self-control exhibited by addicts can certainly be questioned.

Opioids and the Frontal Lobes

Opioid binding in the cortex is highest in anterior regions (Kuhar, Pert, & Snyder, 1973; Lewis, Mishkin, Brown, Pert, & Pert, 1981; S. P. Wise & Herkenham, 1982), and endogenous and exogenous opioids have inhibitory postsynaptic effects at these receptor sites (Koob & Bloom, 1988). Opioids also inhibit cell firing in the locus coeruleus, which has major noradrenergic projections to the prefrontal cortex (Arnsten et al., 1996), and opioids stimulate dopamine release in the prefrontal cortex (Vezina et al., 1992). As might be expected, then, recent evidence similar to that described earlier for cocaine indicates that the frontal lobes may be especially sensitive to opiates such as heroin and morphine. Human PET brain-imaging studies of opiate intoxication in polydrug abusers indicated that morphine, like cocaine, reduces overall cerebral metabolic activity with significant regional reductions in frontal areas (London, 1989; London et al., 1990). More recently, a study of opioid addicts using SPECT indicated significantly lower frontal lobe activity in methadone maintenance patients compared with a control sample of nonaddicts (Krystal et al., 1995). Other physiological measures have also yielded results suggesting relatively selective frontal lobe effects of opioids. For example, electrophysiological studies of opioid modulation of selective attention have implicated opioid-binding sites in the prefrontal cortex (Arnsten et al., 1983). In nonaddicts, the opioid antagonist naloxone was found to increase electrophysiological indices of selective attention at frontal cortical sites only (Arnsten, Neville, Hillyard, Janowski, & Segal, 1984). An EEG study of heroin addicts showed a progressive increase in frontal lobe theta wave activity over the course of repeated relapses to heroin addiction (El Azayem, Abdeen, Gunaidy, & Amin, 1991), and psychophysiological studies of optical tracking in opium addicts were interpreted as reflecting acute and chronic disruption of left frontal lobe functions by opium (Volkov & Mashkova, 1993).

In addition to the aforementioned evidence from psychophysiological and brain-imaging research on opioids, results of a few neuropsychological studies are further suggestive of frontal lobe dysfunction in opioid intoxication and addiction, although there have been some negative findings as well (see Zacny, 1995). Korin (1974) reported that heroin users exhibited elevated perseveration scores on the Bender–Gestalt compared with nonopiate polydrug users. Hill, Reyes, Mikhael, and Ayre (1979) reported that performance of current opioid (heroin or methadone) users was impaired compared with controls on the Category Test of the Halstead–Reitan Battery but improved to control levels following a period of abstinence. In contrast, alcoholics showed a greater impairment that was not reversed by abstinence. Strang and Gurling (1989) reported that a sample of opioid addicts in Britain showed very poor performance on the Maudsley Category Sorting Test, which is derived from the WCST. As more than half of the participants were current injectors of legal pharmaceutical heroin, Strang and Gurling's finding suggests that opioid intoxication may adversely affect neuropsychological indices of prefrontal cortex functioning, but conclusions were limited by the small sample size and the fact that a few participants had recently detoxified from heroin. In a recent review that did not include the latter two studies, Zacny (1995) tentatively concluded that except for impairments of sustained attention, the acute and chronic effects of pure opioid agonists such as morphine or heroin on cognitive functioning appear to be minimal. However, he also noted that much more work needs to be done in this area before any firm conclusions can be reached, especially concerning the impact of opioids on higher cognitive functions, which has been inadequately tested to date.

Neuropsychological Correlates of Chronic Opioid Use

The possibility of chronic neuropsychological effects of opioids was suggested in a report by Grant et al. (1978). Significant correlations between neuropsychological impairment and use of specific drugs in a treatment sample of polydrug abusers were obtained only for sedatives and opiates. This finding could conceivably reflect a preexisting impairment that predisposed certain persons to preferentially abuse sedatives or opiates, although the authors argued against such an interpretation. A subsequent study (Rounsaville, Novelly, Kleber, & Jones, 1981) corroborated the findings of Grant et al. of a high prevalence of neuropsychological impairment among opiate addicts, but the impairment was associated with factors such as alcohol and cocaine abuse and childhood ADHD in their sample. Interestingly, predrug dopamine activity in the prefrontal cortex of rats significantly predicted subsequent morphine self-administration rates in a study by Glick et al. (1992), suggesting that individual differences in prefrontal cortical functioning might be related to opiate addiction liability. Although neuropsychological impairment has not been consistently observed in samples of opiate addicts (Rounsaville, Jones, Novelly, & Kleber, 1982; Zacny, 1995), Petry et al. (1998) recently reported that chronic heroin addicts undergoing outpatient treatment scored more poorly than controls on a new neuropsychological test that can distinguish patients with ventromedial prefrontal cortex lesions from non-brain-damaged controls. In the Bechara card task, heroin addicts, like individuals with prefrontal cortex damage, tended to choose cards that yielded immediate gains but delayed net losses, whereas nonaddict controls tended to choose cards that yielded small immediate rewards and losses but delayed net gains. Heroin addicts also scored significantly lower than controls on measures of future orientation, showing a shortened time horizon compared with controls, perhaps accounting for the tendency of

addicts to act on the basis of immediate rather than delayed consequences (including the potential delayed negative consequences of heroin use, such as the risk of contracting HIV, going to prison, or undergoing opiate withdrawal). Petry et al. noted that their findings were consistent with a deleterious effect of chronic heroin addiction on the frontal lobes, a premorbid frontal lobe deficit in addicts, or exacerbation of premorbid frontal lobe deficits by heroin. They pointed out that deficits in time horizon appear to be partially reversible by treatment, which implies that the problem may to some extent constitute an effect of chronic opiate abuse. Interesting in this regard is the finding that prefrontal lesions lead to a marked reduction in food hoarding behavior in laboratory animals (Kolb, 1977), a possible animal analogue of the deficit in future orientation reported in humans with prefrontal lesions and in addicts as well.

Consistent with the notion that chronic heavy opioid abuse may have deleterious effects on the frontal lobes, a recent postmortem investigation revealed signs of neuronal damage in the frontal cortices of chronic heroin addicts (Garcia-Sevilla et al., 1997). Similarly, in Liu et al.'s (1998) MRI study of abstinent polysubstance abusers, the number of years of heroin use was highly negatively correlated with both prefrontal cortex volume and prefrontal cortex white matter volume. The frontal perfusion deficits observed in abstinent heroin addicts by Rose et al. (1996) at 1 week following heroin discontinuation were only partially reversed when a second SPECT scan was taken 2 weeks later, parallelling the similar findings for abstinent cocaine addicts described earlier. Rose et al. noted that a vascular explanation of their results is not tenable in this case because heroin, unlike cocaine, has minimal effects on vascular tone. They speculated that their findings are consistent with either a short-term neuroadaptive (withdrawal) response of locus coeruleus hyperactivity (which in animal studies is associated with inhibition of frontal cortex), a direct neurotoxic effect of heroin on cortical neurons, or possibly the neurotoxic effects of other drugs such as alcohol or cocaine (although the heroin addicts in their study denied major abuse of other drugs, including alcohol).

Gerra et al. (1998) recently examined cerebral blood flow using SPECT in heroin addicts who had been abstinent for 4 months. They found only a trend for frontal perfusion deficits in addicts versus nonaddict controls, but when addicts were subdivided into clinically depressed and antisocial personality disorder subgroups, significant perfusion deficits were obtained for the right frontal lobe in addicts compared with both controls and addicts without a comorbid psychiatric disorder. The authors suggested that such perfusion deficits linked with psychiatric disorders are likely to have predated the onset of heroin use. However, although depressed addicts also displayed perfusion deficits in the left temporal lobe—consistent with previous studies of clinically depressed nonaddicts—the authors pointed out that the right frontal perfusion deficits they observed in depressed addicts do not generally characterize depressed nonaddicts. A recent computerized tomography study examined relatively "pure" heroin addicts who were devoid of comorbid psychiatric disorders and undergoing outpatient addiction treatment (Pezawas et al., 1998). Signs of cortical volume loss were found in addicts compared with controls; more interestingly, frontal volume loss was significantly greater in addicts who had relapsed within the previous 12 months than in those who had remained abstinent. The authors concluded that "one possible pattern of quick relapse might be poor self-control, loss of foresight, and immature judgment, which are known as psychopathological symptoms of prefrontal volume loss" (p. 145). They invoked heroin-induced neural injury as the most likely explanation of the observed frontal volume loss but acknowledged the possibility that factors other than direct drug effects could be involved. Further work is clearly needed to assess the impact of chronic opioid use versus comorbid psychiatric conditions on the frontal lobes and other higher brain regions, as well as the possible functional and behavioral consequences of such changes.

Tobacco Dependence and Nicotine

Tobacco dependence has presented a bit of a paradox for addiction theorists because there is neither obvious euphoria nor major withdrawal symptomatology associated with the use of tobacco or nicotine (Jarvis, 1994; Lyvers, 1998). Many smokers do, however, report that tobacco withdrawal is associated with negative effects including a decreased ability to concentrate, whereas smoking or nicotine improves concentration (Warburton & Wesnes, 1978). Lyvers, Boyd, and Maltzman (1988) suggested that the difficulty in concentration commonly reported by nicotine-deprived heavy smokers, and their relatively poor vigilance performance, might reflect a nicotine-reversible functional impairment of frontal lobe-mediated attentional processes during the abstinent state. In an indirect test of this idea, Lyvers and Miyata (1993) found that SCR-ORs to novel stimuli were depressed by nicotine deprivation in heavy smokers, whereas smoking elevated these SCR-ORs to the level of nonsmoker controls. Unlike the results previously described for alcohol that used a similar paradigm (Lyvers & Maltzman, 1991a), there was no stimulus-specific drug effect on SCR-ORs to signal stimuli; only SCR-ORs to novelty were affected. Although recent brain imaging studies have reported significant positive correlations between SCR-ORs to novel nonsignal stimuli and prefrontal cortex size and metabolism, interpretation of drug effects on SCR-ORs is complicated by the fact that the prefrontal cortex includes areas with both excitatory and inhibitory influences on SCR-ORs (see Raine & Lencz, 1993; Sequeira & Roy, 1993). Perhaps relevant to Lyvers and Miyata's findings of depression of SCR-ORs to novelty in abstinent smokers, dorsolateral prefrontal lesions disrupt the N200–P300 electrocortical responses to novel stimuli (R. T. Knight, 1984), which are thought to be related to the OR. Prefrontal lesions are also known to render human patients and laboratory animals more susceptible to the deleterious effects of distractors on attentional performance (Chao & Knight, 1995; Goldman-Rakic, 1993). Lyvers and Miyata's findings thus seem generally consistent with the hypothesis of Lyvers et al. (1988) that the distractibility and concentration difficulties that constitute primary features of

tobacco withdrawal may result from hypoarousal of the frontal lobes during acute nicotine abstinence. Lyvers, Maltzman, and Miyata (1994) additionally found that nicotine-deprived heavy smokers exhibited a significantly higher percentage of perseverative errors on the WCST than either nonsmokers or smoking smokers, which is further consistent with a mild disruption of frontal lobe functioning during acute nicotine deprivation.

Perhaps significantly, nicotine binding in the cortex is highest in frontal regions as revealed by PET in human smokers (Nyback, Nordberg, Langstrom, Halldin, & Sedvall, 1989). Nicotine also acutely activates dopaminergic neurons of the ventral tegmental area (Corrigall, Coen, & Adamson, 1994) and promotes release of dopamine from the axon terminals of the mesolimbocortical dopamine system (Picciotto, 1998), and brain reward thresholds are elevated during nicotine withdrawal in rats (Epping-Jordan, Watkins, Koob, & Markou, 1998). Such findings suggest that tobacco dependence may involve the same dopaminergic mechanisms implicated in alcoholism, cocaine addiction and opioid dependence. However, the psychophysiological and neuropsychological findings described above imply that certain frontal lobe functions are depressed or otherwise mildly disrupted during nicotine withdrawal but are acutely facilitated by nicotine, in contrast to the actions of alcohol, cocaine, and opiates, all of which acutely depress frontal lobe functioning. Nicotine's direct agonist action at excitatory nicotine receptors in the frontal cortex might be expected to produce an initial activation that could override or obscure the inhibitory postsynaptic effects of nicotine-induced dopamine release in this region. Indeed, excitatory cortical effects of nicotine are supported by many EEG studies, and signs of cortical hypoarousal accompany nicotine abstinence in heavy smokers (Herning, Jones, & Bachman, 1983; Knott, 1979; Knott & Venables, 1977; Szalai, Allon, Doyle, Peng, & Zamel, 1986; Warburton, 1992). Both smoking-related cues and cigarette smoking increased signs of frontal cortical activation in a recent EEG study of smokers, with smoking cues predominantly activating the left frontal lobe and cigarette smoking predominantly activating the right frontal lobe (Zinser, Fiore, Davidson, & Baker, 1999). Nevertheless, a recent brain-imaging study reported that cerebral glucose metabolism was globally reduced by nicotine in humans (Fowler & Volkow, 1998), paralleling similar findings cited earlier for cocaine and morphine. By contrast, a recent functional MRI study of smokers (Stein et al., 1998) revealed that intravenous nicotine had a direct activating effect on the orbital, medial, and dorsolateral prefrontal cortex as well as portions of the temporal and occipital cortices, accompanied by subjective reports of a "rush" or "high." The frontal areas were among the brain regions most strongly activated by nicotine. The divergent findings of EEG, cerebral metabolic and functional MRI studies of the cortical effects of nicotine could possibly be related to the rapid desensitization of cortical nicotine receptors following acute agonist stimulation (Feldman, Meyer, & Quenzer, 1997), perhaps leading to a more enduring hypoarousal of the cortex that outlasts the initial activation response and that might therefore be more likely to show up on measures with relatively poor temporal resolution, such as PET, whereas measures with a short temporal resolution, such as functional MRI, would be sensitive to nicotine's initial activating effect. In any case, further brain-imaging studies are needed to determine the specific temporal changes in regional brain activity that are associated with acute nicotine and tobacco–nicotine withdrawal before any firm conclusions can be drawn concerning the brain correlates of nicotine use and dependence. Moreover, nicotine may be somewhat different from the other drugs of abuse discussed in the present article because nicotine acts as a "cognitive enhancer" (Picciotto, 1998), and this effect may be a significant factor in tobacco use and dependence.

Other Psychoactive Drugs

An important point in the present context is that not all psychoactive drugs appear to exert selective actions on the frontal lobes. Benzodiazepines, for example, depress cortical metabolic activity in the occipital lobes more than other cortical regions (Buchsbaum et al., 1987) and reduce rather than increase forebrain dopamine release (Di Chiara, 1995). Benzodiazepines also reportedly impair neuropsychological test performance for tests that are sensitive to posterior but not frontal cortical lesions (Golombok, 1989). Perhaps significantly, long-term use of benzodiazepines for anxiety, insomnia, or other disorders typically results in signs of physical dependence but is rarely associated with addictive behavior, that is, compulsive drug-taking associated with drug craving and loss of control (King, 1994; Roache & Meisch, 1995). In this regard, benzodiazepines can be contrasted with alcohol, which similarly acts as an indirect agonist at GABA-A receptors. A crucial physiological difference between these drugs in relation to their addiction potential may be that, as noted above, alcohol additionally enhances, whereas benzodiazepines inhibit, the release of dopamine from the mesolimbocortical dopamine system.

Furthermore, not all psychoactive drugs that *do* appear to exert relatively selective actions on the frontal lobes can be meaningfully described as addictive. Psychedelic drugs, for example, have selective excitatory effects on prefrontal cortex activity, apparently due to agonist actions at excitatory postsynaptic serotonin receptors (Vollenweider, Scharfetter, Leenders, & Angst, 1994). In high doses, these drugs acutely induce a kind of subjective loss of control that is quite different from the sort associated with addiction. A psychedelic "trip" is usually accompanied by an acute subjective loss of normal voluntary or "ego" regulation of mental processes, perceptions, and emotions (Grinspoon & Balakar, 1979). Vollenweider and his colleagues (Vollenweider et al., 1994, 1997) described recent PET studies that showed that the psychedelic drug psilocybin, as well as another type of hallucinogen, the dissociative anesthetic ketamine (an N-methyl-D-aspartate [NMDA] receptor antagonist), selectively increased frontal lobe activity, inducing what the researchers termed a *hyperfrontal metabolic pattern* associated with self-reports of hallucinations and ego loss. A hyperfrontal pattern was also observed in acutely

hallucinating (but nonintoxicated) schizophrenics, in contrast to the hypofrontal pattern more commonly observed in persons with chronic schizophrenia manifesting predominantly negative symptoms (see Volkow & Fowler, 1992). Although psychedelic drugs are not addictive, in that their use is generally sporadic and rarely if ever associated with self-reports of drug craving or compulsive drug-taking behavior, these most profoundly mind-altering of all drugs do appear to exert major selective actions on the frontal lobes—but those actions are excitatory, in contrast to the inhibitory cortical effects of addictive drugs such as alcohol, cocaine, and opioids.

Other human brain-imaging studies have indicated that marijuana and its main active agent, tetrahydrocannibinol (THC)—a much milder consciousness-altering drug that acts at cannabinoid rather than serotonin or NMDA receptors—selectively increases cerebral blood flow and metabolic activity in the prefrontal cortex and cerebellum. The increase in activity in these areas is correlated with the self-reported subjective intensity of intoxication (Adams & Martin, 1996; Volkow, Gillespi et al., 1991). Such marijuana-induced "hyperfrontality" (Nahas & Latour, 1991) is consistent with the cortical distribution of cannabinoid receptors, which are concentrated in the frontal lobes (Herkenham, 1992). Interestingly, nonintoxicated heavy marijuana users exhibited increased perseveration compared with nonuser controls on the WCST in a recent study by Pope and Yurgelun-Todd (1996). Whether this difference primarily reflected a residual effect of marijuana, an abstinence effect, or a premorbid trait characteristic of the drug-using sample is not known. The neuropsychological correlates of acute and chronic marijuana intoxication and abstinence remain to be determined by further research.

Dopamine, Addiction, and the Frontal Lobes: A Proposed Link

Much of the evidence cited earlier indicates that the frontal lobes are especially sensitive to the acute actions of a variety of commonly abused psychoactive drugs. Such evidence further indicates that alcohol, cocaine, and opioids—drugs that are widely regarded as addictive, in that their use leads to compulsive drug-seeking behavior and impaired self-control over drug intake in a significant proportion of users—acutely depress prefrontal cortical activity and, at least in the case of alcohol and cocaine, produce impairments on neuropsychological tests that are sensitive to frontal lobe functioning. Chronic deleterious changes in the frontal lobes are also suggested following long-term abuse of these drugs, although the relative contribution of drug effects versus premorbid factors remains to be worked out. In any case, if the prefrontal cortex mediates the complex of interrelated functions that have been variously termed autonomy, volition, and self-control, then drug-induced impairment of such frontal lobe executive functions may plausibly account for the disinhibition and other behavioral changes associated with acute intoxication, as well as contributing to more chronic problems such as impulsiveness, inflexibility, perseveration, denial, and difficulties with self-control described in alcoholics and other addicts. The likelihood of acute and/or chronic frontal lobe deficits in addicts has significant implications for addiction treatment and relapse prevention methods, as has been previously discussed by several authors (Goldman, 1990; Petry et al., 1998; Weinstein & Shaffer, 1993).

A possible neurochemical mechanism of drug addiction was recently described by Robinson and Berridge (1993; but see Gawin & Khalsa-Denison, 1996, for a critique of some aspects of this theory), who proposed that addictive behavior reflects progressive drug-induced sensitization of dopamine circuits mediating attribution of incentive salience to relevant stimuli. Enduring sensitization of dopaminergic neurotransmission by chronic ingestion of so-called addictive drugs has been clearly demonstrated in laboratory animals (Carlson & Almasi, 1979; Di Chiara, 1995; Vezina et al., 1992), and also recently in human heroin addicts through the apomorphine test (Casas, Guardia, Prat, & Trujols, 1995). As described previously, the inhibitory postsynaptic actions of dopamine in the prefrontal cortex are probably a significant determinant of the frontal lobe effects of such drugs. A few preliminary models have thus been offered that have attempted to link chronic drug-induced sensitization of mesolimbocortical dopamine circuits to chronic dysfunction of the prefrontal and (in particular) orbitofrontal cortex and associated impairments of behavioral self-regulation in alcoholism (Modell et al., 1990) and cocaine addiction (Volkow et al., 1996). As discussed earlier, these models postulate that such sensitization leads to hyperactivity of the orbitofrontal region, yet brain-imaging and other relevant data are clearly more consistent with acute drug-induced and chronic hypoactivity of this area in addicts. Thus a more plausible interpretation of the findings to date is that the drug-elicited hyperdopaminergic state induces a general hypoactivity of the prefrontal cortex (including the orbitofrontal, dorsolateral, and medial areas), a condition associated with perseverative tendencies and relatively disinhibited, impulsive, and poorly self-controlled behavior. Future functional brain-imaging studies should assess intoxicated and nonintoxicated addict and control participants under conditions that normally activate the prefrontal cortex (such as performance of the WCST) in order to better evaluate the acute and chronic frontal lobe effects of addictive drugs.

Highly relevant to the present discussion is a recent review (Arnsten & Goldman-Rakic, 1998) of the prefrontal cortex dysfunction elicited by stress-induced hyperdopaminergic states in nonhuman primates. Arnsten and Goldman-Rakic postulated that the mesocortical dopamine system essentially serves to take the prefrontal cortex "off-line" during stressful events so that faster, more automatic or instinctive responses mediated by posterior cortical and subcortical areas can control behavior. This general interpretation of mesocortical dopamine function has important implications for addiction processes. Acute depression of prefrontal activity due to excessive inhibitory mesocortical dopaminergic neurotransmission evoked by drugs such as cocaine or alcohol, increasingly accompanied over time by sensitization of such dopaminergic neurotransmission and perhaps chronic neurotoxic drug or dopamine actions on the

frontal lobes, should significantly reduce the inhibitory control exerted by prefrontal cortical areas over posterior cortical and subcortical systems mediating reinforcement and "automatization" of behavior (Tiffany, 1990). Such a process could readily lead to many of the behavioral changes associated with addiction, including the definitive feature of impaired control over drug use.

In summary, many abused psychoactive agents appear to exert relatively selective actions on the frontal lobes. Most drugs that are meaningfully regarded as addictive (according to current definitions emphasizing compulsive usage patterns and loss of control) tend to produce acute decreases in frontal lobe activity whether the drugs are classified as stimulants or depressants. By contrast, hallucinogenic or mind-altering drugs, which are generally considered much less addictive or nonaddictive (Gable, 1993), appear to increase frontal lobe activity. Both types of abused psychoactive chemicals apparently disrupt frontal lobe functioning, but in quite different ways, producing rather different behavioral manifestations. Well before the opposite actions of these different drug classes on the gross activity of the frontal lobes were known, some radical approaches to the treatment of drug addiction and alcoholism used—with uncertain success—intense psychedelic drug experiences to break the cycle of addictive behavior (see Grinspoon & Balakar, 1979, and more recently, Halpern, 1996). Psychedelics, which act as agonists at excitatory postsynaptic serotonin receptors in the cortex (Jacobs, 1987), have also been reported to relieve symptoms of OCD (Leonard & Rapaport, 1987). More recently, the class of antidepressants known as selective serotonin reuptake inhibitors have been used to treat OCD symptoms (Greist, 1990) and to reduce alcohol consumption in alcoholics (Gorelick & Paredes, 1992; Naranjo, Kadlec, Sanhueza, Woodley-Remus, & Sellers, 1990) with indications of some limited success thus far (see Higley et al., 1998), although they appear to be ineffective as a treatment for cocaine addiction (Grabowski et al., 1995). The rationale for this treatment approach is based on the hypothesis that a pre-drug, inherited dysfunction involving the serotonergic innervation of the prefrontal–orbitofrontal cortex characterizes at least some OCD patients and addicts (Cloninger, 1987; Conrod et al., 1997; Heinz et al., 1998; Higley & Linnoila, 1997; Higley et al., 1996, 1998; LeMarquand et al., 1998; Nielsen et al., 1998; Pihl & LeMarquand, 1998; Pihl et al., 1995; Virkkunen et al., 1995, 1996; Virkkunen & Linnoila, 1997). For reasons discussed previously, a premorbid serotonergic deficit would be expected to render such individuals relatively more susceptible to the dopaminergic actions of drugs such as alcohol, cocaine, and opiates, a possible predisposing factor in addictions.

In an earlier assessment of the concept of self-regulation as it pertains to addiction issues, W. R. Miller and Brown (1991) lamented the fact that the important issue of volition has largely been neglected by experimental psychology. They noted that disruption of frontal cortical functioning generally leads to impairment of volition or self-control processes and that a variety of evidence suggested that signs of frontal lobe dysfunction accompany both acute drug intoxication and addiction. However, Wilkinson (1991) pointed out that one possible problem for a "frontal lobe" hypothesis of addiction is that it offers no obvious reason why the impairment of control should be specific to drug taking. Patients with prefrontal lesions, after all, exhibit an apparent loss of autonomy in their seemingly automatic or stereotyped responses to a wide variety of stimuli. Although the disinhibition induced by addictive drugs such as alcohol and cocaine is indeed observed in a variety of contexts, and drug addicts and alcoholic individuals tend to display deficient behavioral self-regulation in general (as discussed earlier), specific impairment of control over drug taking is nonetheless a central defining feature of addiction irrespective of other behavioral changes. However, the "frontal lobe" hypothesis of addiction does not intrinsically require that the drug-induced changes in some prefrontal cortex neurons and synapses be functionally equivalent in all respects to gross frontal brain damage. Various recent biological approaches to addiction (e.g., Kreek & Koob, 1998; Ridley, 1994; Robinson & Berridge, 1993; Tiffany, 1990; Wise & Bozarth, 1987) emphasize the role of chronic, sensitized dopaminergic drug actions in subcortical areas such as the nucleus accumbens and striatum as the primary basis of an "acquired drive" that sporadically manifests as drug "craving" or "wanting." Such drive states can be triggered by drug-related stimuli or by the direct effects of the drugs themselves—the well-known priming effects of drugs and drug cues (de Wit, 1996; Stewart, 1984). As discussed previously, the prefrontal cortex is normally capable of regulating subcortical processes because of its extensive modulatory interactions with subcortical areas, yet such regulation is diminished when the prefrontal cortex is actively inhibited by the very process it would otherwise modulate. Thus, drug urges may not need to be particularly strong to overcome resistance and trigger resumption or continuation of drug taking when the primary basis of behavioral self-regulation in the brain is subdued by the same subcortical system that gives rise to drug "craving" or "wanting"—specifically the mesolimbocortical dopamine system, which innervates subcortical areas implicated in drug drives (such as the nucleus accumbens, striatum, and amygdala) as well as the executive prefrontal cortex, which is essential for behavioral flexibility and self-control. In other words, drive may be released by the actions of dopamine on subcortical areas, whereas control processes are simultaneously inhibited by dopamine at the cortical level. Though necessarily simplistic (reflecting the current primitive level of understanding of brain–behavior relationships), this answer to the problem raised by Wilkinson is entirely consistent with Arnsten and Goldman-Rakic's (1998) hypothesis that the mesocortical dopamine system serves to take the prefrontal cortex temporarily "off-line" so that faster, more automatic or instinctive responses mediated by subcortical and posterior cortical areas can direct behavior.

The frontal lobe hypothesis of addiction does not obviate a major role of premorbid vulnerabilities in addictive disorders; indeed, such predispositions appear to significantly involve frontal cortical processes as well, as I have frequently noted. Interactions with psychosocial and environmental influences are also indicated given that stress stimu-

lates and sensitizes dopamine release in the mesocortical dopamine system innervating the prefrontal cortex (Arnsten & Goldman-Rakic, 1998; Kaneyuki et al., 1991; Le Moal & Simon, 1991; Piazza et al., 1996; Thierry, Tassin, Blanc, & Glowinski, 1976). Such hyperdopaminergic effects of stress on the mesocortical dopamine system would be expected to increase susceptibility to addiction and relapse by reducing frontal cortical inhibitory regulation of posterior cortical and subcortical systems mediating incentive responses and automatized behaviors, including those behaviors that have been potently reinforced by drugs. Consistent with this general idea, footshock stress was recently reported to selectively reinstate cocaine- but not food-reinforced responding following extinction in laboratory animals (Ahmed & Koob, 1997). The frontal lobe perspective on addiction thus can readily accomodate an interactive, multifactorial, biopsychosocial interpretation of the pathogenesis of addictive behavior.

In any case, the evident parallels between some aspects of drug addiction and disorders of the frontal lobes, together with the recent evidence of frontal lobe effects of addictive drugs, have significant implications for the debate between advocates and detractors of the popular notion that addicts are characterized by a true (if relative) loss of control over their drug use. In particular, if the prefrontal cortex is indeed in some sense the neural basis of self-control, then frontal lobe dysfunction under the acute and chronic influence of drugs might plausibly account for the impaired control over drug use that defines addiction.

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