The orbitofrontal cortex (OFC) plays a central role in human behavior. Anatomically connected with association areas of all sensory modalities, limbic structures, prefrontal cortical regions that mediate executive function and subcortical nuclei, this brain region can serve to integrate the physical and emotional attributes of a stimulus-object and establish a motivational value based on estimation of potential reward. To the extent that addictive disorders reflect a dysregulation of the ability to evaluate potential reward against harm from drug self-administration, it would be anticipated that substance abuse disorder might reflect dysfunction of the OFC. With the application of brain imaging techniques to the study of human substance abuse, evidence has been obtained that activity in the OFC and its connections plays a role in several components of the drug-rewarding behavior of substance abuse, including expectancies, craving and impaired decision making.

The orbitofrontal cortex (OFC), a paralimbic region, participates in association functions, integrating emotion with behavior and various sensory processes (Hof et al., 1995). Its dysfunction has been implicated in psychiatric disorders that involve inappropriate emotional and behavioral responses to stimuli. The best example is that of obsessive compulsive disorder (Rauch et al., 1994; Breiter and Rauch, 1996; Zald and Kim, 1996), but post-traumatic stress disorder (Semple et al., 1993), disorders of mood (Pardo et al., 1993; Baker et al., 1997), antisocial personality disorder (Meyers et al., 1992) and aggression (Fornazzari et al., 1992; Siever et al., 1999) are also included. Although symptoms may overlap among these and other disorders (e.g. compulsive drug-seeking by addicts, reminiscent of behavior that characterizes obsessive compulsive disorder), the range of pathologies linked to the OFC supports its central role in human behavior. More specifically, the OFC contributes to a variety of behavioral states and functions, including the processing of reward, emotion and decision making (Bechara et al., 2000; Rolls, 2000; Schultz et al., 2000), which are essential components of motivational-directed behavior. The motivational values can be innate (such as the drive for food); or they may be learned with repeated reinforcement. Substance abuse, which can be conceptualized as a dysregulation of motivational-directed behavior, is an example of the latter case.

The OFC is placed in a position to code the motivational attributes of responses to stimuli. It is a heterogeneous region that has connections with other prefrontal, limbic, sensory and premotor areas (Cavada et al., 2000; Öngür and Price, 2000). Linked to the mesolimbic dopamine system that is critical for drug reward (Di Chiara and Imperato, 1988; Koob and Bloom, 1988; London et al., 1996; Wise, 1996), it receives inputs from association areas of each sensory modality (olfactory, gustatory, visual, auditory and somatosensory) (Pandya and Yeterian, 1990; Morecraft et al., 1992; Cavada et al., 2000; Öngür and Price, 2000). Therefore, the OFC has the information needed to integrate the sensory characteristics of a stimulus-object (Carmichael and Price, 1996). The OFC can attach an emotional valence to the stimulus-object through its relationship with the amygdala (Barbas and De Olmos, 1990; Morecraft et al., 1992). Furthermore, it can evaluate these characteristics against previous experience through its connections with regions known to subserve memory (dorsolateral prefrontal cortex and mediadorsal nucleus of the thalamus, pars magnocellularis (Morecraft et al., 1992; Ray and Price, 1993), hippocampus and hippocampal gyrus (Cavada et al., 2000; Öngür and Price, 2000)). Finally, the OFC–striatum–globus pallidus–thalamus–OFC loop (Alexander and Crutcher, 1990) can mediate reinforcement of the motivational attribute of a stimulus-object.

A modular approach to the role of the OFC, although heuristic, may help tease out the various mechanisms that mediate substance abuse. Using such a strategy, individual components of aberrant behavior in substance abusers can be studied separately. One of these components is expectancy that is based on predictions of reward and attribution of probabilistic rewarding properties to the stimulus-object. Another is compulsive drive (motivational state) to use drugs, which is linked to craving. Lastly, decision making, based on the motivational attributes of the stimulus and the balance between expectation of immediate reward and long-term losses, is an important aspect of substance abuse behavior.

While considering how the OFC is involved in these three behaviors, it is important to appreciate the heterogeneous nature of this region, histologically and anatomically (Morecraft et al., 1992; Carmichael et al., 1994). Anatomically, the OFC can be divided into anterior regions, which connect with higher association cortices (such as the dorsolateral prefrontal cortex), and posterior regions, which have selective connections with the amygdala, and entorhinal and perirhinal cortices. Therefore, anterior regions schematically would be important in decision-making processes, and posterior regions in the emotional and autonomic aspects of craving. Both regions could contribute to expectancy, which depends on the evaluation of the emotional valence of the stimulus. Along a transaxial plane, the medial OFC is connected with the ventral striatum and the lateral OFC is connected with the caudate nucleus, which suggests that the medial OFC would be more important to reinforcement than the lateral OFC.

This review covers findings from brain imaging studies that support important contributions of the OFC to the persistent behavioral states characteristic of addiction. To date, most functional imaging studies have been unable to distinguish accurately between the different regions of the OFC that might take part in the respective behaviors. The enhanced spatial resolution of new generation positron emission tomography (PET) scanners and improved technology of functional mag-
OFC Metabolism in Polysubstance Abusers: Personality Traits, Expectancy and Motivation

PET studies, performed to elucidate abnormalities in brain function that might contribute to the perpetuation of addiction, have provided evidence for dysfunction of the OFC in drug abusers. In one of these studies, regional cerebral metabolic rate for glucose (rCMRglc), an index of local brain function (Sokoloff et al., 1977; Phelps et al., 1979; Reivich et al., 1979), was measured in polydrug abusers and in control subjects who were drawn from the same community (Stapleton et al., 1995). Twenty polydrug abusers took part in a study of the acute effects of cocaine on rCMRglc, measured using PET with the [18F]fluorodeoxyglucose (FDG) method (London et al., 1990). Polydrug abusers completed two test sessions, one in which cocaine was administered and another in which saline (placebo) was given. Ten control subjects, recruited for comparison, also participated in two PET sessions, but never received cocaine. Measures of rCMRglc during only the placebo administration were used for comparison with data from control subjects. To avoid order effects on rCMRglc (Stapleton et al., 1997), data from only those drug abusers (n = 10) who received placebo in their first PET session and data from the first PET session of the control subjects (n = 10) were used. Although the substance abusers did not know whether they would receive placebo or cocaine for their first session, control participants knew that they would receive placebo for all sessions. Prior to the PET scan, each substance abuser participated in four preliminary test sessions, two with placebo and two with cocaine (20 and 40 mg i.v.), in order to acquaint them with the subsequent test procedures.

Mean global metabolic rate for glucose (mg/100 g tissue/min) in the substance abusers (6.91 ± 0.17) did not differ significantly from the rate in the control group (7.27 ± 0.21), but the pattern of rCMRglc differed between the two groups. Visual inspection of the brain images revealed that control participants showed relatively uniform cortical glucose metabolism compared with the substance abusers, whose rCMRglc was reduced in posterior regions (Fig. 1). When metabolic rate data for each region were submitted to analysis of covariance with the global metabolic rate as a covariate, the substance abusers showed higher glucose utilization than the control group in the OFC, superior frontal gyrus, middle temporal gyrus and insula (Table 1, Fig. 1). Notably, the greatest group difference was in the OFC (Stapleton et al., 1995). Of the ten substance abusers, six met criteria for antisocial personality disorder and one met criteria for pathological gambling. Therefore, differences in rCMRglc of the OFC between the groups could reflect psychological characteristics associated with substance abuse. This view is consistent with previous findings of abnormal rCMRglc of OFC in individuals diagnosed with disorders of behavioral control.

Figure 1. Images of rCMRglc in a selected subject from a group of polydrug abusers (right, n = 10) and a group of control subjects who were not substance abusers but were drawn from the same population (left, n = 10) (Stapleton et al., 1995). The arrow points to the orbitofrontal gyrus, which exhibited significantly higher rates of rCMRglc in the substance abuse group when metabolic rates were adjusted for global metabolism. Drug abuse subjects also showed higher adjusted rCMRglc in the superior and middle temporal gyri.
adjusted for global glucose metabolism as indicated in Materials and Methods. Abusers may have shown conditioned drug effects, as they had the typical conditions of drug self-administration, the substance context of expectancy of drug reward. Such integration can be with an interpretive response to placebo administration in the (and also in temporal and superior frontal areas) is consistent 1982a,c). In this light, elevated rCMRglc in the OFC and insula tempopolar component, provides integration between extra-brain region in patients with personality disorders characterized by a high level of impulsivity and aggressiveness (Siever et al., 1999).

Emotional state, related to expectancy of drug reward, may have also been reflected in the higher rCMRglc in the OFC of the substance abusers. As they took part in a double-blind procedure in which the injection could have been placebo or cocaine, they likely experienced a negative emotional reaction (e.g. disappointment) when they realized that they had received placebo. In contrast, control participants would not have been as likely to have this emotional response. This interpretation is supported by our findings from a recent study (Grant et al., 1996) in which normalized rCMRglc was negatively correlated with self-reported mood in a number of OFC regions when neutral (not drug-related) visual cues were presented.

The elevated rCMRglc in other cortical areas (insula, temporal lobe and superior frontal gyrus) in addition to OFC in the substance abusers suggests that the response to the placebo injection included activation of a circuit related to a component of motivation. Classic work of Mesulam and Mufson in the old world monkey has demonstrated connections between the OFC and insula, which also receives projections from the temporal pole and other paralimbic areas (Mesulam and Mufson, 1982a–c). On the basis of this and other work, these authors suggest that the paralimbic brain, particularly its insulo-orbito-temporopolar component, provides integration between extra-personal stimuli and the internal milieu (Mesulam and Mufson, 1982a,c). In this light, elevated rCMRglc in the OFC and insula (and also in temporal and superior frontal areas) is consistent with an interpretive response to placebo administration in the context of expectancy of drug reward. Such integration can be critical to the ‘motivational state’ or drive to use drugs.

Although the PET study situation was markedly different from the typical conditions of drug self-administration, the substance abusers may have shown conditioned drug effects, as they had previously received cocaine under test conditions that were in some ways similar to the PET session. Thus, the higher rCMRglc as compared with control values may reflect activation in response to conditioned, drug-related cues (i.e. an injection given by an investigator who administered cocaine previously in a test situation). Nonetheless, substance abusers also exhibit higher normalized rCMRglc under conditions where there are no drug-related cues or expectancy of drug administration. A supplementary analysis of the data collected in our study of cue-elicited cocaine craving (Grant et al., 1996) compared rCMRglc in seven OFC brain regions of substance abusers and controls only in the session where a non-drug (arts and crafts) stimulus complex was presented. Drug abusers exhibited a significantly higher normalized rCMRglc than controls in the medial prefrontal cortex.

Role of the OFC and its Connections in Drug Craving

In addition to the aforementioned evidence that the OFC shows an abnormality in rCMRglc, which may be related to some degree to conditioned responses and motivation, findings obtained with PET and fMRI have suggested that activation of the OFC and its connections accompanies cocaine craving (Table 2). Although it is not definitively proven that the activation reported reflects the mechanism by which craving is induced, the findings are consistent with an integrative function of the OFC, as supported by its anatomical connections. It is tempting to speculate that activation of cortical regions with sensory and limbic functions, along with activation of the OFC, reflects an interplay of related networks. Thus, sensory information about environmental (or internal) stimuli might be interpreted at the level of the OFC, which connects with the amygdala in evaluating the motivational value of the stimuli, and labeling the emotional response as craving.

One approach to the study of the neurobiological substrates of craving has involved the induction of craving by presentation of stimuli that have previously been associated with drug use. There is substantial evidence that exposure to cues, such as the paraphernalia used during drug self-administration, which are strongly associated with previous drug taking, can trigger craving for drugs of abuse (Childress et al., 1992).

Our research group studied cue-elicited cocaine craving in cocaine abusers (n = 13) and control participants (n = 5), who were presented with a stimulus complex, including a cocaine-related videotape and paraphernalia in one session and a videotape and objects related to arts and crafts in another session (Grant et al., 1996). We also measured rCMRglc by the FDG method and PET. Exposure to cocaine-related cues produced self-reports of craving and activation in the medial OFC and five other composite cortical brain regions in cocaine abusers: dorsolateral prefrontal, peristriate, temporal/parietal, retrosplenial and temporal (see Fig. 2). Furthermore, self-reports of craving were positively correlated with metabolic increases in the dorsolateral prefrontal cortex, medial temporal lobe (amygdala) and cerebellum. These effects were not seen in non-drug-abusing control participants. The activation pattern seen in our study, involving the OFC and several areas to which it is linked anatomically, is consistent with an integrative function of OFC, involving brain areas that participate in sensory processing (peristriate cortex) and episodic memory (dorsolateral prefrontal cortex and temporal areas), as well as emotional coding (amygdala).

Childress et al., by assay of regional cerebral blood flow (rCBF) with 15O-labeled water, also investigated the response to

Table 1

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Control Left</th>
<th>Control Midline</th>
<th>Control Right</th>
<th>Substance Abuse Left</th>
<th>Substance Abuse Midline</th>
<th>Substance Abuse Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe</td>
<td>6.07</td>
<td>6.00</td>
<td>6.17</td>
<td>6.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>6.59</td>
<td>6.19</td>
<td>7.26</td>
<td>7.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>7.84</td>
<td>8.09</td>
<td>8.54</td>
<td>8.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>8.61</td>
<td>8.23</td>
<td>8.66</td>
<td>8.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>10.10</td>
<td>9.81</td>
<td>10.53</td>
<td>11.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aEach value is the mean regional cerebral metabolic rate for glucose (rCMRglc, mg/100 g/min), adjusted for global glucose metabolism as indicated in Materials and Methods.

bGroup factor: Substance Abuse different from Control, P < 0.05.

cLaterality factor: Left different from Right, P < 0.05.

ABInteraction of Group by Laterality factors, P < 0.05.
exposure to cocaine-related cues (Childress et al., 1999). While watching a cocaine-related videotape, cocaine users experienced craving and showed a pattern of increase in limbic (amygdala and anterior cingulate) normalized rCBF and decreases in basal ganglia normalized rCBF relative to their responses to a neutral videotape (nature film). These findings generally supported our previous observations (1996) in demonstrating that limbic activation accompanies cue-induced cocaine craving, but did not show activation of the OFC or the dorsolateral prefrontal cortex. Differences in experimental conditions

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Study</th>
<th>Treatment effects</th>
<th>Correlations with craving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug administra tion</td>
<td>Cocaine-induced craving</td>
<td>fMRI (Breiter et al., 1997)</td>
<td>nucleus accumbens, subcallosal cortex, striatum, basal forebrain, thalamus, cingulate, parahippocampal gyrus, lateral prefrontal cortex, striate/extrastriate (increases)</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate-induced craving in cocaine abusers</td>
<td>PET rCMRglc (Volkow et al., 1999)</td>
<td>anterior cingulate, right thalamus, cerebellum</td>
</tr>
<tr>
<td>Cue-induced craving</td>
<td>Cocaine cues</td>
<td>PET rCMRglc (Grant et al., 1996)</td>
<td>dorsolateral prefrontal cortex, medial OFC, temporal/parietal, peristriate, temporal, retrosplenial</td>
</tr>
<tr>
<td></td>
<td>Cocaine cues</td>
<td>fMRI (Maas et al., 1998)</td>
<td>anterior cingulate, left dorsolateral prefrontal</td>
</tr>
<tr>
<td></td>
<td>Cocaine cues</td>
<td>PET rCBF O 15 (Childress et al., 1999)</td>
<td>amygdala and anterior cingulate (increased) basal ganglia (decreased)</td>
</tr>
<tr>
<td></td>
<td>Cocaine cues</td>
<td>PET rCMRglc (Wang et al., 1999)</td>
<td>medial OFC, left insula, cerebellum</td>
</tr>
<tr>
<td>Spontaneous craving</td>
<td>For cocaine</td>
<td>PET rCMRglc (Volkow et al., 1991)</td>
<td>medial OFC</td>
</tr>
<tr>
<td></td>
<td>For cocaine</td>
<td>PET rCMRglc (Grant et al., 1996)</td>
<td>medial prefrontal cortex (relative to control subjects)</td>
</tr>
</tbody>
</table>

Figure 2. Images of rCMRglc, determined in a selected cocaine abuser (from a group with \( n = 13 \)), during two test sessions in which either neutral (left) or cocaine-related (right) stimuli were presented (see Grant et al., 1996). The subjects abstained from cocaine use for at least 36 h before each assay of rCMRglc. The figure shows pseudo-colored metabolic (PET) images superimposed on the respective structural (MRI) images. The arrow points to the medial orbitofrontal cortex (MO), which exhibited a significant increase in rCMRglc during the active cues session. Subjects also showed increases of rCMRglc in other cortical regions (temporal lobe, TL; parahippocampal gyrus, PH; peristriate cortex, PS) and reported cocaine craving. In contrast to the metabolic increases in the cocaine abuser group, control subjects tended to show decreases in rCMRglc.
The OFC and Decision Making in Drug Abusers

In light of the aforementioned evidence for a functional contribution of the OFC to expectancy states and drug craving, it is of interest to determine how dysfunction of this brain region might also influence cognitive processes, particularly decision making in substance abusers. Despite the behavioral alterations associated with OFC lesions, patients with such brain damage failed to show impairments on classic neuropsychological tests of frontal lobe function (Stuss et al., 1998; Bechara et al., 2000). However, novel tasks that can serve as specific probes for the functional role of the OFC have been developed (Freedman et al., 1998; Bechara et al., 2000).

As a first step toward determining whether drug abusers have a functional deficit involving the OFC, we have utilized a task that was specifically designed to evaluate human patients with lesions of the ventromedial portion of the OFC (VmAOFC) (Bechara et al., 2000). Patients with these lesions demonstrate generally irresponsible behaviors, including poor judgement in business and personal decisions. The Gambling Task was developed to capture these traits in a laboratory setting by...
requiring subjects to make choices based on the long-term consequences of complex reward/punishment contingencies. The task is performed as a card game in which the participant selects cards from four decks that differ with respect to the payoff for each card selection and the frequency and severity of penalties, indicated by certain cards. It has face validity for drug abuse since poor performance results from making choices that yield large short-term rewards even when such choices eventually lead to net losses. Indeed, one of the DSM IV criteria for substance abuse disorder states (on p. 181) that ‘substance abuse is continued despite knowledge of having a recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance’ (American Psychiatric Association, 1994). Similarly, the World Health Organization (1992) uses the criterion for disorders due to psychoactive substance use of ‘persisting ... despite harmful consequences’ (p. 321). Although the Gambling Task models some aspects of drug abuse behavior, the balance between reward and negative consequences differs somewhat from the real life situation of the drug abuser. One difference is the fact that the certainty of reward is greater when considering self-administration of a drug than taking a card in the model task.

In our study, polydrug abusers were compared with a group of subjects who did not use illicit drugs of abuse (Grant et al., 2000). The scores on the GT were nearly 50% lower in drug abusers (n = 50) than in controls (n = 24), but not as low as those of patients with VmOFC lesions (Bechara et al., 1994). In contrast to GT results, there was no difference in performance between drug abusers and controls on the Wisconsin Card Sorting Task, which is sensitive to lesions of the dorsolateral prefrontal cortex but not the OFC (Stuss et al., 1998). These results support the working hypothesis that there is a functional abnormality, as opposed to a frank lesion, specifically in the ventromedial prefrontal cortex of drug abusers, but not necessarily in the frontal lobe as a whole. Further, they are consistent with the notion that the OFC is linked to the ability to balance short-term gains against longer-term consequences in the process of decision making.

Other studies have also shown that drug abusers are likely to make maladaptive decisions when faced with short-term versus long-term outcomes, especially under conditions that involve risk and uncertainty. In one of these, opioid-dependent participants placed less value on delayed monetary rewards than control subjects (Madden et al., 1997), underscoring the concept that drug abusers are overly biased towards the immediate value of rewards and less able to evaluate the consequences of their actions in the future. In another study, amphetamine abusers, opiate abusers, non-drug-using comparison subjects and patients with VmOFC lesions were tested on a decision-making task similar to the Gambling Task (Rogers et al., 1999). Amphetamine users and lesion patients performed more poorly than subjects in the other groups, although the amphetamine users did not do as badly as the lesioned patients. Furthermore, there was a negative correlation between task performance and years of stimulant use. Interestingly, experimentally induced depletion of tryptophan, the precursor of the neurotransmitter serotonin, in non-drug-using comparison subjects led to impaired task performance. These results suggest that specific classes of drugs of abuse may have a differential impact on the processes underlying decision-making abilities, and the impact may be influenced by the drug’s effect on serotonergic, and perhaps other aminergic, neurotransmission.

Our research group has begun a series of experiments to investigate whether impaired performance on the Gambling Task in drug abusers is directly due to dysfunction of the VmOFC. The aim of the first set of studies was to demonstrate that the VmOFC is involved in Gambling Task performance in neurologically intact subjects. We therefore conducted PET assays of rCMRglc during performance of the Gambling Task. Preliminary results from seven subjects indicate that the level of performance on the Gambling Task is positively correlated with activation of the VmOFC (Grant et al., 1999) (see Fig. 3). These results suggest that successful Gambling Task performance requires anatomical integrity as well as adequate metabolic activity of the VmOFC. Our results are convergent with those of previous neuroimaging studies showing activation of the ventromedial prefrontal cortex in subjects who had to guess about task-related reward contingencies (Elliot et al., 1997) or in subjects who experienced violations in expectancies (Nobre et al., 1999; Elliot et al., 2000).

It is important to emphasize that these imaging studies do not preclude the participation of other brain regions in complex decision making, especially regions with anatomical connections with the VmOFC. For example, in our study, there was also a strong positive correlation (r = 0.93) between rCMRglc in the amygdala and Gambling Task performance. This is consistent with the recent demonstration of impaired performance on the Gambling Task in patients with amygdala lesions (Bechara et al., 1999). As reviewed in the previous section, work in our laboratory (Grant et al., 1996) and others (Table 1) has implicated the amygdala in behavioral processes related to addiction, such as craving. Having obtained a preliminary description of the brain circuitry associated with Gambling Task performance, we have initiated PET studies to test the hypotheses that during performance of the Gambling Task, drug abusers will exhibit little or no activation in the VmOFC or other relevant brain regions, such as the amygdala.

Conclusion
This review presents findings of neuroimaging studies that implicate the OFC in several behavioral aspects of substance abuse, including anticipation of drug reward, craving for the drug, and possible impairments in judgement that could influence the decision to abstain or take the drug. For example, cocaine-abusing research participants have manifested elevated normalized rCMRglc in the OFC when they were in a test situation where they anticipated possible cocaine administration but were drug-free. Furthermore, the OFC and some of its afferents (e.g. amygdala, insula) showed activation when drug abusers are presented with drug-related cues, such as videotapes or their own audiotapes relating their drug experiences, which induced drug craving. Craving induced by psychostimulant drug administration was also correlated with changes in signal measured from the amygdala in a fMRI study and with normalized rCMRglc in the OFC. Lastly, individuals with recent histories of drug abuse show impairment on cognitive tasks that require decision making, particularly the Gambling Task, their performance appearing to be related to activation of the OFC. The extent to which differences between substance abusers and naive control subjects, particularly related to the function of the OFC, reflect a pre-existing condition, which confers vulnerability to addiction and promotes its perpetuation, is not known. Although unproven, it is reasonable to hypothesize that the negative consequences of drug abuse may include a negative impact on the function of the OFC. If this were the case, drug
abuse would damage the very substrates of brain function that are required for recovery.

The initial impression from the work reviewed supports the view that the OFC, through its anatomical connections with sensory and limbic systems, serves as a critical 'node' in the processing of environmental and internal cues to generate feeling states that influence the motivation to seek and self-administer a drug. Even if this inference ultimately were proven to be true, however, several important tasks would still lay before us. We would need to identify the neural networks that code for the different behavioral components of substance abuse, such as drug expectancy, craving, and impaired decision making. It then would be important to characterize the role of the OFC in these networks as primary or secondary; and to evaluate the contribution of possible dysfunction of the OFC to the deviant behaviors of substance abuse (e.g. necessary but insufficient, sufficient but not necessary, or insufficient and not necessary). A final step would be identification of the neurochemical messengers that operate in the networks. Even before these tasks are tackled, however, it is important to consider the findings reviewed above in the design of therapeutic approaches for substance abuse. This instruction is particularly relevant to the implementation of a cognitive therapy that would require executive functioning that requires integrity of the OFC and its connections.

Notes
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American Psychiatric Association (1994) Diagnostic and statistical manual


