Cognitive and neuropsychopharmacological processes in human drug craving
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Drug Craving and Addiction: Integrating Psychological and Neuropsychopharmacological Approaches

In the present review, an integrated approach on craving and addiction is discussed which is based on recent insights from psychology and neuropsychopharmacology. An integrated model explains craving and relapse in humans by the psychological mechanism of "attentional bias" and provides neuropsychopharmacological mechanisms for this bias. According to this model, cognitive processes mediate between drug stimulus and the subject's response to this stimulus and subsequent behavioral response (e.g. drug use, relapse). According to the model, a conditioned drug stimulus produces an increase in dopamine levels in the corticostriatal circuit, in particular the anterior cingulate gyrus, amygdala, and nucleus accumbens, which in turn serves to draw the subject's attention towards a perceived drug stimulus. This process results in motor preparation and a hyperattentive state towards drug-related stimuli that, ultimately, promotes further craving and relapse. Evidence for this attentional bias hypothesis is reviewed from both the psychopharmacological and the neuroanatomical viewpoint. The attentional bias hypothesis raises several suggestions for clinical approaches and further research.


Introduction
Recent models of addiction have provided well-described, testable theories of addictive behavior. Many recent theories of addiction contain the concept of incentive motivational processes. Incentive motivation can be defined as a cognitive and affective state triggered by stimuli associated with the perception of unconditioned stimuli. According to the incentive motivation model, and supported by a host of empirical evidence, drug-related stimuli are able to elicit classically conditioned responses in drug addicts, both physiologically and subjectively (e.g. "craving"). In most current conceptualizations of drug dependence, subjective craving is regarded as a central phenomenon, contributing to the continuation of drug use in active addicts and the occurrence of relapse in detoxified addicts. Furthermore, cognitive factors such as memory processes, expectancies, and attentional processes are recently added to the range of cue-elicited reactivity. At the moment, one of the major theoretical challenges in the addiction field is to gain knowledge on the neurobiological and cognitive processes behind the classically conditioned relation between drug stimulus and craving. In historical perspective, the field of cognitive psychopharmacology has been employing psychopharmacological agents as tools to study the mechanisms underlying cognitive functions or to study cognitive (neuropsychological) deficits such as consequences of long-term drug abuse. However, from a cognitive neuroscience point of view, cognitive processes are studied because of their mediating role between neuropsychopharmacological processes and behavior. Cognitive processes represent an essential link between stimulus, pharmacological processes and response (see also). In the last decade, studying hypotheses of addiction mechanisms in animals has resulted in an impressive knowledge about addiction. And although the utilization of "cross-domain integration", i.e. testing animal-derived hypotheses in humans, is believed to become the rule rather than exception in cognitive neuroscience, up to now there are few signs of this "cross-domain integration" in human addiction research.

In the current review, recent insights from psychopharmacology and cognitive psychology are discussed and an integration of these theoretical accounts is promoted. It will be discussed that cognitive processes mediate between drug stimulus and the subject's ini-
tial response to this stimulus on the one hand and his subsequent behavioral response (e.g. drug use, relapse) on the other. From these cognitive processes, enhanced attentional processing of these drug-related stimuli (attentional bias) is thought to play a central role. This attentional bias is in essence an automatic process that does not need conscious processing of the stimuli.

Neurobiological research shows that drug related stimuli are able to elicit a (classically conditioned) increase in dopamine levels in the brain. While it has long been postulated that dopamine acts by directly producing euphoric or pleasurable feelings, recent suggestions have been made that dopamine primarily serves to draw a person’s attention to events which predict or signal reward, such as a drug-related stimulus.

In the current paper, evidence will be discussed that a) attentional focusing on drug related cues is enhanced in drug abuse patients; b) that this is the result of dopaminergic activity; c) this elicits craving and promotes drug use. Furthermore, it will be discussed that these processes are important key-concepts for understanding addictive behaviors and an integration of the psychological and neurobiological models is proposed.

The current review and hypotheses are largely based on findings from opiate, stimulant, and alcohol studies. The intrinsic addictive aspects share common neurocognitive mechanisms. Whenever possible, studies using human participants will be discussed. Furthermore, although involvement of other neurotransmitter systems such as the 5-HT system, endorphin system and GABAergic system in drug craving are reported, the current view is primarily focused on dopaminergic systems.

First, a short overview on craving in humans and its role in addiction is presented to give a general understanding of the model. Secondly, the concepts of attention and selective attention are described and models of attentional bias for emotional cues and drug cues are discussed. In addition, the question whether this attentional bias for appetitive cues can occur outside consciousness is addressed. Thirdly, the psychopharmacological underpinnings of the attentional processes are outlined: in particular, the role of dopamine in craving experiences and selective attention is discussed. Fourth, the common neuroanatomical substrates of craving and attention are described. Fifth, the implications of the model for clinical aspects are discussed, together with an overview of the model.

Psychological Approaches

Craving is an emotion

In the field of human addiction research, several reviews have been published in which the concept of craving is outlined. From these reviews it becomes clear that there exists little consensus on the concept of craving. It has been argued that the term craving should be reserved for states of extreme desire. However, this restriction is rather artificial and results in a dichotomous representation of the concept (craving is present or absent), a situation that is not analogous to other psychological phenomena, such as depression and anxiety that can be measured on a continuous scale. For research purposes, it is more appropriate to interpret craving as a continuous measurable state that, in addition to pathological states, can also be present in non-addicted subjects.

The desire for drugs is often regarded as an abnormal subjective motivational state that is the result of substance dependency. In the early days of psychology, motivational states were seen as the result of a homeostatic dysregulation. The drive was seen as a regulator of internal body states. Within the homeostatic dysregulation theory, craving was seen as the need to establish a new homeostasis after drug withdrawal. It was thought that motivational aspects of internal states were “simple” biological needs and therefore could be excluded from “the emotions”. Emotion researchers such as Frijda noticed that in the most prominent emotion theories, desire is not regarded as an emotion. However, it can be argued that desire is the emotion that accompanies approach behavior; in the same way that fear is the emotion that accompanies avoidance behavior. From recent studies it has become clear that,
In addition to unconditioned stimuli, conditioned stimuli play a central role in motivational learning and the accompanying emotional components (incentive motivation). Incentives act as triggers to restate drug use behavior or, at least, elicit craving. Within this incentive motivational framework, craving is (just as food cravings and sexual desires) a conditioned appetitive motivational state. Drug craving, food craving and sexual desire are all affective states that are results of the appetitive processes (see also\textsuperscript{129}). Drug craving fits well within the definition of emotion as proposed earlier by Gray\textsuperscript{74}: "...states produced by instrumental reinforcing stimuli" (rewards and punishers, including changes in rewards and punishers). Addictive behavior is the result when the brain's approach mechanism is hypersensitized (see also\textsuperscript{46}). Craving can be seen as the accompanied emotional state that is produced by conditioned stimuli that are associated with the reward effects of substances or behavior. In humans, different appetitive processes (including drug craving) probably share common neuronal pathways\textsuperscript{80}. Also in recent cognitive theories of emotion, the traditionally differentiated processes of motivation and emotions are regarded as different viewpoints of the same cognitive process\textsuperscript{174} which is mediated by the same brain systems (see below and \textsuperscript{13}).

In contrast to emotions in the "desire spectrum", there is a vast database of knowledge on fear-related emotions and psychopathology\textsuperscript{116}. Although knowledge of desire-related emotions and the psychopathology of approach behavior is growing\textsuperscript{124} there is a need for theoretical and clinical progress in building valid models of desire-related psychopathology.

\textbf{Attention for emotions}

Attention is one of the important cognitive constructs which are a requisite for adaptive behavior. Not every stimulus that is offered to a subject has to be transformed into a mental representation. Selection of relevant information from all available information is necessary. If no selection were made, humans would act in a non-goal-directed fashion upon every single stimulus or thought. The attentional system plays also a major role in the human emotional system. Attention is, par excellence, the mechanism by which salient (aversive or appetitive) stimuli are inventoried by an organism. In order to survive, an organism has to approach (unconditioned) pleasant stimuli such as food and water, and has to avoid (unconditioned) unpleasant stimuli such as extreme heat. By means of associative (classical) conditioning animals learn which associated cues signal pleasant and unpleasant stimuli. This conditioned incentive motivational process results in approach responses elicited by conditioned appetitive stimuli, and avoidance responses elicited by conditioned aversive stimuli. Attention is automatically directed towards cues that predict reward or punishment (cues with motivational significance). The relation between attention and motivation can be regarded as different perspectives on a common phenomenon\textsuperscript{132}. Attention, as well as motivation and emotion, serve as preparation for action: approach or avoidance of significant stimuli.

Although there is no general accepted definition of attention, it can basically be divided into two categories, a non-specific general state of arousal (as in vigilance) and selective attention. If using the term attention in this paper, only the latter category, i.e. selective attention, will be meant. Selective attention is a cognitive function which facilitates the processing of relevant stimuli and inhibits the processing of less relevant stimuli. Selective attention is a vast category and includes several (anatomically distinct) functions such as modulation of the orienting response (OR) and voluntary focusing. Numerous classifications of selective attention have been made\textsuperscript{118,153,162}. However, detailed discussion of theoretical categories of attention falls beyond the objectives of the present paper. There is, however, one important subclassification that can be distinguished within the concept of selective attention, i.e. voluntary
(active; directed; top-down, controlled) or involuntary (reactive; passive; bottom-up; automatic) attention. Voluntary attention is involved when a person actively searches out stimuli that have personal relevance. Although both selective attention mechanisms will be discussed, the role of automatic selective attention in addiction will be emphasized. In this process, attentional allocation is based on stimulus salience and directed in a bottom-up fashion according to the relative salience. Involuntary attention is automatically involved when a person is exposed to surprising, novel, threatening, or unexpected stimuli. This adaptive function of the selective attention mechanism increases the likelihood that most appropriate stimuli will control behavior. Furthermore, it is important to note that controlled voluntary attention is inversely proportional to automatic attention. During a directed attention task, a person can be distracted by a stimulus that elicits an automatic orienting response which disrupts the ongoing directed attention.

If the brain could process all available information, attentional mechanisms would not be needed. To protect the brain from overload, attention is understood as a "limited capacity mechanism". When measuring attentional bias, i.e. the automatic (hyperattentive response to relevant stimuli, one can make use of this limitation of capacity. That is, the more attention that is focused (voluntary or involuntary) on a secondary task or stimulus, the less cognitive capacity is available for the primary task. Indeed, most operationalizations of attentional processes in humans utilize this limited capacity of the brain in experimental tests (dual task measurement). One of the most frequently used dual task paradigms to measure attentional bias is the emotional Stroop task. In this task, the subject is asked to name the color in which a word with emotional content (e.g. fear) is printed (primary task). What is generally observed in this task is that the voluntary controlled task (color naming) is interrupted by an automatic attentional process, the subject is distracted by the emotional content of the word (secondary stimulus). As a result, reaction times (RTs) of color naming are slower on words with an emotional content. For example, research shows that, compared to healthy subjects, spider phobics are more distracted by the content of spider-related words than by neutral words. Recent studies indicate that this implicit process operates very quickly, the attentional bias being present even when the emotional word is not consciously perceived in order to be selectively processed. This preconscious processing of emotional stimuli is frequently investigated with the masked Stroop paradigm. The emotional stimulus is presented to the subject for a brief period of time (about 20 msec), and is immediately replaced by a mask. These studies show the same attentional bias as the unmasked task, although less pronounced.

**Signaling reward: Attentional bias for incentives**

As with the extensive literature on the neurobiological pathways of the emotions fear and anxiety, cognitive studies on attentional processing of anxiety cues have made a major contribution to the understanding of the human avoidance system (for overviews). In summary, these cognitive data show the presence of biases in selective attention to threat-relevant information in anxiety. From overviews it becomes clear that the neurobiological pathways responsible for this attentional bias, including the processing of threatening information and subsequent motor-preparation in order to avoid this threat, are for a great part understood. In addition, the psychiatric treatment of anxiety disorders, including pharmacological, cognitive and behavioral treatments, has been relatively successful compared to treatment of less understood disorders such as addictive behaviors. Although research addressing the cognitive neuroscience of appetitive information processing has been neglected for some time, the need for cognitive neuroscience models of the approach system has recently been stressed by several authors. Just like fear related emotional disorders, increasing fundamental knowledge of the appetitive "approach system" will eventually result in im-
proved treatment of desire related disorders such as addictions.

One of the striking aspects of addiction is the preoccupation of drug users with drugs and drug related cues. Preoccupation with these cues can be conceptualized as an attentional bias. Drug stimuli become more and more wanted and receive more and more attention. Or as Robinson & Berridge state: "...they become especially salient stimuli, stimuli that grab attention, that become especially attractive and wanted, thus eliciting approach and guiding behavior to the goal".

To date, few studies have addressed the cognitive processing of appetitive or pleasant information. Several studies (using different techniques) indicate that, analogous to fear-related information, attentional bias for positively valenced stimuli is present. Some studies show that the processing of appetitive/pleasant information has an effect on cortical measures of attention such as event-related potentials (ERPs) and startle electromyography (EMG). Other studies provide indications that behavioral measures of attention (reaction times) are affected by the presence of appetitive stimuli. All these studies show that, in addition to negative (fearful) stimuli, positive (appetitive/pleasant) stimuli also have attention-grabbing properties. Since drug stimuli have also appetitive/incentive positive properties, at least within drug-dependent subjects, the same methodologies can be applied to test the hypothesis that drug stimuli have attention-grabbing properties. The evidence for this hypothesis this will be discussed in the next section.

**Attentional bias for drug cues**

There is ample evidence for the presence of an attentional bias in addiction-related disorders, including alcohol dependence, nicotine dependence, cocaine dependence and opiate dependence. Table 1 summarizes these studies on attentional bias in substance abuse disorders. In line with a general model of the relation between emotional, motivational and attentional processes, attentional bias is also observed in other abnormal motivational states that elicit approach behavior, such as compulsive gambling and eating disorders. Neurophysiological evidence for the enhanced attentional processing of drug cues comes from event-related potential (ERP) studies. Analysis of the stimulus-induced changes in the ERP provides important indications that drug cues enhance cognitive processing. Alpha frequency bands of the spontaneous EEG of polydrug abusers were desynchronized during exposure to cocaine stimuli. Although these authors interpreted the results in terms of the rather indeterminate term "cortical arousal", there is sufficient evidence that changes in the background EEG (particularly, desynchronization of alpha frequencies and synchronization of beta frequencies) are related to changes in the attentional state elicited by external or internal (emotional) stimuli. Synchronization of the beta rhythm during watching of smoking stimuli is also found in a previous study. Event-related potentials (ERPs) are a second indicator of attentional processes that can be derived from the EEG. For example, enhanced late positive ERP responses provide an indication of enhanced attentional processing of emotional cues. Several studies have shown that this ERP component was enhanced for alcohol, smoking, cocaine and heroin cues in a population of substance-dependent subjects. In addition the Pre-Pulse Inhibition (PPI) paradigm is frequently used to study both controlled and automatic attentional processes in normals and in schizophrenics. Hutchinson and colleagues demonstrated that the presence of smoking cues decreases PPI among smokers, possibly by enhancing attention for these cues and thereby decreasing attention for the prepulse. Furthermore, there are preliminary data on the information processing of alcohol cues indicating that exposure to alcohol cues increased PPI.
The involvement of attentional processes in addictive behavior is in some aspects in accordance with the cognitive processing model of Tiffany\(^2\). Tiffany suggested that drug-use behavior in the addict is largely controlled by automatic processes. According to his model, craving is a non-automatic cognitive process, which is only activated by the interruption of the automatic drug use behavior. Cepeda-Benito & Tiffany\(^3\) found some evidence for this hypothesis: Cue-elicited craving disrupts performance on a RT task.

The latter finding was also found in studies on cognitive capacity during exposure to drug-related stimuli\(^1^{10,11}\). However, more specifically than Tiffany's model, the present view hypothesizes that craving itself is not responsible for the disruption of the secondary task, but rather the accompanied attentional bias for drug-related stimuli.

**Is attentional bias an implicit cognitive process?**

The attentional processing of salient stimuli is

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Attentional bias finding</th>
<th>Relation to craving</th>
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<tbody>
<tr>
<td>Johnson et al., 1994</td>
<td>Word-Stroop</td>
<td>Alcohol, Attentional bias for alcohol-related words in abstinent alcoholics</td>
<td>Not measured</td>
</tr>
<tr>
<td>Stetter et al., 1995</td>
<td>Card Word-Stroop</td>
<td>Alcohol, Attentional bias for alcohol-related words in abstinent alcoholics</td>
<td>Not measured</td>
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<tr>
<td>Stormark et al., 1997</td>
<td>Word-Stroop</td>
<td>Alcohol, Attentional bias for alcohol-related words in alcoholics</td>
<td>Not measured</td>
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<tr>
<td>Bauer &amp; Cox, 1998</td>
<td>Word-Stroop</td>
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<td>Not measured</td>
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<tr>
<td>Cox et al., 1999</td>
<td>Word Stroop</td>
<td>Alcohol, Attentional bias for alcohol-related words in heavy drinkers</td>
<td>Not measured</td>
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<tr>
<td>Stormark et al., 2000</td>
<td>Probe detection</td>
<td>Alcohol, Attentional bias for alcohol-related words in abstinent alcoholics</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sharma &amp; Albery, 2001</td>
<td>Word-Stroop</td>
<td>Alcohol, Attentional bias for alcohol-related words in problem drinkers</td>
<td>Not measured</td>
</tr>
<tr>
<td>Cox et al., 2002</td>
<td>Word-Stroop</td>
<td>Alcohol, Attentional bias for alcohol-related words in non-successful alcoholics in treatment</td>
<td>Not measured</td>
</tr>
<tr>
<td>Ryan, 2002</td>
<td>Word-Stroop</td>
<td>Attentional bias found in both alcoholics (also in controls)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Rosse et al., 1993</td>
<td>Visual scanning</td>
<td>Cocaine, Not reported</td>
<td>Correlation between visual scanning length of cocaine pictures and craving</td>
</tr>
<tr>
<td>Rosse et al., 1997</td>
<td>Visual scanning</td>
<td>Cocaine, Not reported</td>
<td>Correlation between fixations on cocaine picture and craving</td>
</tr>
<tr>
<td>Franken et al., 2000a</td>
<td>Probe detection</td>
<td>Cocaine, No attentional bias</td>
<td>Correlation between RTs on cocaine cues and craving</td>
</tr>
<tr>
<td>Lubman et al., 2000</td>
<td>Pictoral probe detection</td>
<td>Opiate, Attentional bias for opiate pictures</td>
<td>No correlation between attentional bias and craving</td>
</tr>
<tr>
<td>Franken et al., 2000b</td>
<td>Word-Stroop</td>
<td>Opiate, Attentional bias for heroin words, but not for subliminal presented words</td>
<td>Correlation between RTs on heroin cues and craving</td>
</tr>
<tr>
<td>Gross et al., 1993</td>
<td>Card Word-Stroop</td>
<td>Nicotine, Attentional bias for nicotine-related words in abstinent smokers</td>
<td>Not measured</td>
</tr>
<tr>
<td>Johnsen et al., 1997</td>
<td>Word Stroop</td>
<td>Nicotine, Attentional bias for nicotine-related words in smokers</td>
<td>Not measured</td>
</tr>
<tr>
<td>Waters &amp; Feyerabend, 2000</td>
<td>Word-Stroop</td>
<td>Nicotine, Attentional bias for nicotine-related words in smokers</td>
<td>Not measured</td>
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<td>Ehman et al., 2002</td>
<td>Dot-Probe</td>
<td>Nicotine, Attentional bias for nicotine-related words in smokers</td>
<td>Not measured</td>
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The term unconscious is often associated with Freudian terminology, especially in addiction research. However, there are clear differences between the Freudian unconsciousness and the cognitive unconsciousness. The automatic nature of drug use has been demonstrated before. The role of awareness in the automatic processing of drug-related stimuli is scarcely addressed. In addictive behaviors, it is recognized that drug approach can be observed in the absence of conscious craving. For example, Robinson and Berridge note that the neural system responsible for incentive attribution can produce goal-directed behavior in the absence of conscious awareness of "wanting" itself. Recent information processing theories of emotion suggest the existence of goal-driven actions upon non-conscious perceived emotional stimuli. There is ample evidence that very brief (below perception threshold: subliminal) presentation of emotional information can influence behavior unconsciously (preconscious processing). For example, the preconscious processing of a subliminal presented aversive stimulus (e.g. a 15 msec presentation of a fear-related stimulus) results in an anticipatory behavior of the subject which is reflected in an increased attention towards the stimulus and altered behavioral measures such as increased reaction time. Neurobiological studies show that there are subcortical "quick and dirty" neuronal routes which process emotional information preconsciously. Currently, there is sufficient evidence for non-conscious cognitive processes which are involved in the fear processing. The involvement of a non-conscious process in appetitive processing is not yet fully elucidated. There are indications that the processing of appetitive stimuli may be as rapid as the processing of aversive stimuli as result of a general cognitive processing phenomenon of all emotional stimuli. A few studies addressed this issue.
other motivated behavior such as feeding and sexual behavior in male rats. Most of these dopamine studies have been conducted in animals. Few studies address the role of dopamine in motivated behavior of humans. Human studies on dopaminergic involvement are scarce, probably due to the limitations imposed by ethical limits. There is some evidence from case studies that dopamine agonists result in enhanced sexual desire. Furthermore, there are reports that dopamine antagonists disturb appetitive motivational behavior, such as sexual desire. The role of dopamine antagonists in the human motivation for food is unclear. Clinical observations indicate that neuroleptic agents increase appetite. It may be that this increase is the result of antagonistic effects of neuroleptics on the D2 receptors in the perifornical lateral hypothalamus, that are opposite to the effects of dopamine antagonists on appetite in mesolimbic areas. This effect, however, may be the result of non-dopaminergic factors such as 5-HT involvement (weight gain is more often reported with a-typical neuroleptics than with typical neuroleptics), and hyperprolactinemia-induced changes in insulin sensitivity. These studies in humans are in line with the more general role of dopamine in the incentive motivation process.

A role for dopamine in human drug craving

This section presents a summary and discussion of the literature on the relation between dopamine and craving. Besides postmortem tissue studies on dopaminergic markers and positron emission tomography (PET) studies, use of dopaminergic agents is one of the few ways to study the role of dopamine in humans. Therefore, human studies which examine the role of dopamine in motivated behavior are scarce. In animal studies on dopamine antagonists, it was found that dopamine antagonists reduce both appetitive-approach motivation towards rewards and diminishes the reinforcing effects of rewards. Although many brain processes are comparable, not all results from animal studies apply to humans. For example, the finding that dopamine antagonists reduce the reinforcing actions of stimulants in animals is not found in humans. In contrast to the lack of effects on subjective euphoria, dopamine antagonists consistently show to have effects on the motivational aspects of drug and alcohol use (drug wanting). Berger et al. showed that haloperidol, a dopamine antagonist, reduces craving after exposing the cocaine-addicted subject to cocaine-related stimuli. In a naturalistic pilot study, Smelser and colleagues observed a reduced cue-elicited craving in recently withdrawn cocaine addicts after administering risperidone. Gawn and colleagues also observed a reduced craving after treating cocaine addicts with flupenthixol. In addition to the cocaine craving, cue-elicited alcohol craving is also reduced after pretreatment with dopamine antagonists in human subjects. However, few studies employing dopamine antagonists in the treatment of drug addiction have been conducted and yield mixed results or negative results.

Is there a role for dopamine in attention?

One of the hypotheses of the current article is that dopamine triggers the "brain's attention" towards appetitive stimuli in general and, in specific, drug-related cues. It is hypothesized that activation of dopaminergic activity in the corticostriatal reward circuit by cues which signal reward could contribute to one of the characteristics of addiction, i.e. the excessive focus on activities which lead to further drug use. Dopamine release, triggered by stimuli or actions that predict rewarding (or aversive) outcome, is necessary to focus the subject towards these cues, reducing the probability that these cues are ignored. Summarizing, dopamine, among others, triggers attention towards conditioned incentives. Although direct evidence is lacking, peripheral evidence comes from studies that demonstrate the involvement of dopamine in the attentional systems. According to the current hypotheses, should dopamine antagonists, besides modulating drug craving, also modulate human selective attention.

It is known for some time that dopaminergic system is one of the biological underpinnings of the attentional system of the brain, and it has been acknowledged that dopamine is...
involved in normal attentional processes such as selective attention\textsuperscript{5,22,152}, and detecting targets and preparing for an appropriate response\textsuperscript{82}. Disorders associated with reduced dopamine availability, such as Parkinson's disease, display selective attention deficits\textsuperscript{152,796,238}. Furthermore, dopamine antagonists are able to modulate selective attention in healthy volunteers\textsuperscript{111}; however, it is not clear in what direction this modulation is directed. There are indications that manipulation of dopamine functioning in humans can both impair and improve selective attention in a U-shaped manner: either an increase or decrease in dopaminergic activity leads to disruption of selective attention\textsuperscript{102}. Possibly, this depends on personality factors, receptor effects (D1/D2), and used test drugs. Recent studies among healthy subjects showed that even low doses of the dopamine D2 antagonist haloperidol (2 mg oral range) suppressed the electro-physiological response to attended stimuli\textsuperscript{7} and reduced Stroop interference (i.e. improved selective attention)\textsuperscript{232}.

Latent Inhibition (LI) studies show that the dopamine system is associated with attentional functions. LI refers to the retardation of conditioning which occurs if a to-be-conditioned stimulus is first presented a number of times ('preexposure') without other consequences\textsuperscript{77}. LI is considered to reflect the process of selective attention by which an organism screens out irrelevant stimuli\textsuperscript{23,141}. Specifically, LI reflects the ability not to attend to irrelevant stimuli\textsuperscript{23}. There is ample evidence for dopaminergic involvement in LI in animals and in humans\textsuperscript{77,141,154}. The effects of dopamine antagonists on LI may provide an important link between dopaminergic overactivity and cognitive dysfunctions in humans\textsuperscript{158}. Most human studies show that dopamine antagonists potentiate LI, indicating improved selective attention functioning\textsuperscript{143,240,211}. Dopamine agonists generally reduce LI\textsuperscript{115,108,378,202}. These findings are in line with the present hypothesis. When general selective attention is increased (by dopamine antagonists), automatic processes are consequently decreased. Accordingly, (automatic) attention for drug cues will be reduced.

In addition to evidence from LI studies that dopamine is involved in attentional functioning, studies using PPI techniques form another paradigm to study the involvement of dopamine in attention, yet with different neuroanatomy (see\textsuperscript{177}). PPI refers to the robust phenomenon, present in both human and nonhuman animals, that the startle reflex is inhibited when the startle probe (pulse) is preceded by a weaker stimulus (the pre-pulse). In addition to LI, several studies indicate that PPI is altered by dopaminergic agents such as haloperidol and bromocriptine\textsuperscript{1}. However, it is not yet clear how dopamine affects PPI, because both agonists and antagonists are capable of reducing PPI\textsuperscript{109}. It must be added that dopamine is not the only neurotransmitter involved in the regulation of PPI. Although less frequently studied, in animals there are indications that glutamate\textsuperscript{221}, acetylcholine\textsuperscript{102}, and serotonin\textsuperscript{56} systems are, in addition to dopamine, involved in the regulation of PPI. However, there are indications that the regulation of PPI inhibition in humans is modulated by neurotransmitter systems other than in animals. For example, Liechti and colleagues\textsuperscript{170} found that serotonin agonists increased PPI in humans, whereas in rats they decreased PPI\textsuperscript{120}.

Dopamine is also not the only neurotransmitter involved in motivational and attentional processes. The role of other neurotransmitters such as acetylcholine (ACh) and 5-HT in attentional processes involved in addiction has been suggested. Bushnell and colleagues\textsuperscript{85} proposed that the attention-consuming preoccupation with incentive stimuli depends on abnormal increase in the reactivity of cortical cholinergic inputs. They suggested this after the observation that cortical ACh release mediates the overprocessing of a stimulus\textsuperscript{25}. Although studies have indicated that ACh is involved in attentional processes\textsuperscript{179}, this involvement of cholinergic transmitters in the striatum on attentional functioning is not yet clear. There are indications that intra-striatal ACh antagonists do not have a clear impact on attentional functioning of rats, in contrast to dopamine-antagonists\textsuperscript{19}. Although some studies suggest a role for 5-HT in attentional functioning in
animals, in humans selective attention for relevant stimuli seems to be unaffected by serotonergic manipulation. Although no published studies are known that study both attention for drug cues and craving, a recent study indicated that dopamine antagonist haloperidol (2 mg) attenuates enhanced cognitive processing of drug cues in heroin dependence but not craving. Summarized, dopamine antagonists affect selective attention in humans. In addition there are some preliminary indications that they affect appetitive motivational responding in humans (craving, wanting). However, it is not clear whether the reduction in cue-elicited craving as a result of dopamine antagonists is modulated by hyperattentive processing of drug stimuli. Studies on the facilitating or inhibiting effects of dopamine antagonists on human attentional performance are needed to test the specific assumptions of the present model.

Neuroanatomical pathways of craving and attentional processes

There has been an increase of fMRI and PET scan studies on the neuroanatomy of human in recent years. These studies show that the striato-thalamo-orbitofrontal circuit is essential in goal-motivated behaviors. Regions commonly found to respond with an altered function during drug craving, as measured with PET or fMRI scans, include nucleus accumbens, thalamus, striatum, anterior cingulate cortex (ACC), anterior cingulate cortex (ACC), dorsolateral frontal cortex, orbitofrontal cortex, and amygdala. Garavan and colleagues showed that most of these 'craving regions' are not specific dedicated neurocircuits, but are the same regions which are activated by appetitive stimuli (sexual content) in healthy volunteers. It was found that the ACC might be an exception, in that its activation in humans may be specific for the emotional state 'drug craving'. Two recent studies show that the ACC is specifically activated in cocaine addicts during craving, and not during the experience of other emotions.

It is well recognized that regions that are activated during drug craving are, at least in part, the same regions that are activated during a working memory task. In addition, recent studies point to the fact that craving and attentional processes have common neuronal regions. For example, due et al. found evidence that drug cues are processed like rare targets in that they activate attentional brain regions. For some time it has been acknowledged that there are certain regions that are both involved in attentional functioning and cue-elicited craving. Several fMRI and PET scan studies (for an overview see Bush et al. and MacLeod & MacDonal), have shown that the ACC is involved in selective attention. The ACC is activated during cognitive processes that are involved in response competition, such as the stroop task. This region is also frequently found to be involved in cue-elicited cocaine craving. In addition, metabolism in the superior cingulate is increased by dopamine agonists and decreased by antagonists. The latter can be explained by an indirect effect of blocking D2 receptors in the basal ganglia. The ACC has reciprocal connections with the amygdala and nucleus accumbens. The nucleus accumbens and ACC are both part of a corticostriatal circuit involved in stimulus-reward learning. These interconnected regions are probably involved in signaling reward, and a prerequisite for signaling reward is selective attention. In humans, anterior cingulotomy results in disruption of controlled cognitive processing. Based on neuro-psychological testing, the latter authors conclude that the ACC may monitor goal-related significance of stimuli and signal the need of a re-orienting of attention.

Lang and colleagues have suggested that the cingular and amygdalar regions are critical in mediating effects of attention and emotion. Once appetitive (and aversive) cues are identified by the visual cortex, motivational/attentional centers, such as amygdala and ACC, are activated to enhance processing.
Furthermore, after several imaging studies on dopaminergic involvement in cocaine addiction, one of the conclusions of Volkow and colleagues was that abnormal dopaminergic regulation of the ACC might be responsible for the inability to control intake of the drug and the intense desire to take the drug \(^2\). Although the function of intake control is independent of craving, with its own neuropharmacological underpinnings, the ACC may play an important role in the regulating of intake behavior. Arntsen \(^6\) noted that "high levels of catecholamine release during stress may serve to take the prefrontal cortex offline to allow faster, more habitual responses mediated by the posterior and/or subcortical structures to regulate behavior". This may provide an explanation why cue-elicited craving cannot be resisted and leads "automatically" to relapse. As stated above, dopamine is increased in the prefrontal cortex when a drug user is exposed to drug-related stimuli. Following Arntsen, this may impede the prefrontal cortex to control behavioral responses. However, this mechanism is not an explanation for craving and attention but a neuropsychopharmacological explanation for "loss of control" that is frequently experienced by drug addicts, and is therefore beyond the scope of this article.

In addition to the role of the ACC, the role of the amygdala in appetitive and aversive motivated behavior has been stressed \(22,23,42,84,136\). In addition to the "traditional" role of the amygdala in fear conditioning \(17\), there is evidence from a number of appetitive systems (food, sexual, drugs) that the basolateral amygdala is also involved in appetitive conditioning \(48\) and the perception of emotional cues \(47\). Specifically, a correlation has been

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**Figure 1. A possible role of attentional bias in craving and drug use relapse**

Perception drug related stimulus

- Enhanced signaling of drug cues (further processing of the original cue or signaling new cues)
- Increase drug related cognitions (memory bias, obsessive thoughts, preoccupation with drugs)
- No attentional resources left for alternative cues (e.g., control strategies, coping mechanisms)

Increase dopaminergic activity

Attentional bias

Craving

Drug use and relapse
Chapter 1

found between drug craving and amygdalar activation\(^2^3\). As with the ACC, the amygdala also plays a role in the function of selective attention. This function includes the selective attention for both unconditioned reinforcing stimuli and conditioned reinforcing stimuli. Furthermore, the results of Morris et al.\(^2^6\) suggest that the human amygdala mediates the learning of association between behaviorally significant stimuli, even without conscious perception. Summarized, the dopamine system of the corticostrial circuit, in particular the ACC, amygdala and nucleus accumbens, may play an important role in integrating attentional functioning which is necessary for signaling rewards. The resulting hyperattentive state for reward-related stimuli is associated with excessive wanting (craving).

Integration

A cognitive psychopharmacological model

As with cognitive research on the approach system in general, research on drug addiction requires a better understanding of the motivational components of addiction, and the cognitive aspects behind these motivational processes\(^6\). The role of cognitive processes within substance use disorders seem also promising for understanding of complex addiction phenomena, such as drug craving. Several studies show high correlations between drug craving and attentional bias\(^4^2,6,1^6,5\). However, the relation between emotions (craving) and cognition (attentional bias) is complex and assessment of causal relations is difficult. It is widely accepted that emotional states can modulate attentional focusing. However, attentional processes can also modulate emotional processes. For example, MacLeod\(^2^5\) and colleagues showed that attentional bias was able to modify emotional vulnerability and emotional reactions. Although it is not directly tested, this finding makes it conceivable that attentional bias for drug cues can modulate craving and relapse. In the present model it is suggested that attentional bias and craving are able to modulate each other. Nevertheless, as result of the increased dopamine release, attentional bias will first activate the feeling of craving (no craving without attention). This activation of craving will further enhance the attentional bias.

How can attentional bias contribute to drug use and relapse? In general, the presence of attentional bias may contribute to addictive behaviors in three ways (see figure 1; dashed lines/boxes). First, maintenance of addictive behaviors may be the result of an enhanced likelihood to detect and become aware of drug cues in the environment. This automatic selection process is responsible for the process that drug cues are signaled more easily. It is acknowledged that the perception of drug related cues is related to conditioned responses (e.g. craving) that may trigger relapse\(^6\). Second, once a drug cue is detected, it is automatically processed and it is difficult to draw attention away from this cue. Attention-related cognitive processes such as memory bias (an enhanced memory for drug related cues) may contribute to an increased craving\(^6\). It is conceivable that enhanced attentional focusing on drug cues may trigger more explicit cognitive processes such as positive drug related expectancies and intrusive thoughts. Third, because of the limited capacity of attention, the automatic focusing on drug related cues would result in a subsequent failure in the processing of competitive cues. For example, attentional narrowing towards drug cues may explain the "binge use" of drugs. Binging can be seen as a disorder of satiety. In the presence of drug cues bingers ignore (i.e. do not focus attention to) rival cues that may signal this satiety\(^1^1\). Because the automatic nature of this process, it is difficult for the addict to apply attentional resources to (learned) cognitive and behavioral avoidance strategies aimed to prevent relapse.

The present model proposes a cognitive intermediate, attentional bias, in the classically conditioned association between drug-related stimuli craving and relapse. This attentional bias is present during the cognitive processing of drug-related stimuli. Because this cognitive bias is- at least in part- involuntary and unintentional, this suggests the existence of an "automatic" pathway to continued drug use and may provide important clues for the future development of treatment interventions.
Clinical relevance and future studies
The clinical relevance of the model is that both assessment and treatment (relapse prevention) of substance abuse disorders may be improved when paying attention to attentional bias.

Concerning relapse prevention, most current addiction treatment interventions based on classical conditioning, focus on the extinction of (subjectively experienced) craving elicited by exposure to a drug-related stimulus; the model stresses the need to incorporate the extinction of automatic responses in the extinction process. However, to date, it is not clear whether these automatic processes can be modified by therapeutical interventions. When it is possible to gain more control over cognitive processes, cognitive treatment approaches that target drug craving and control over approach behavior may be successful in reducing attentional bias and relapse. In addition, if attentional bias and craving can be demonstrated to result from increased dopaminergic activity, an antagonizing effect of a dopamine agonist on attentional bias and craving would argue for further investigation into specific dopamine antagonists.

In addition to the relevance of the model for the understanding of human craving and for the treatment of addiction, the findings of the present study may contribute to improvements in the assessment of motivation for drugs and drug approach tendency. Recent studies indicate that attentional bias for alcohol and smoking related stimuli is a reliable predictor of relapse in addictive behaviors. This predictive value of attentional bias is supported by the current model. One of the major problems in addiction research is the measurement of addiction-related constructs such as craving. It is known that self-report in general and self-report of motivational states is confounded by voluntary (or involuntary) cognitive strategies. Self-reported craving may provide an incomplete or inadequate index of drug motivation. In addition, motivational aspects that are triggered by appetitive cues are notoriously difficult to measure by self-report alone. It is clear that self-report can not function as the gold standard in measuring subjective experiences such as appetitive motivational states and affective states in general. However, current operationalizations of a subject’s drug approach tendency lean heavily on self-reported craving and/or intention to use, both of which - by definition - depend on a person’s ability to reflect on his internal (motivational) state. One of the major problems in human studies on drug craving is that this self-report can be confounded by factors such as social desirability, which may explain the finding that relapse is often not preceded by craving. Although animal studies of relapse may use a more direct and objective measure of relapse, many of new insights provided by these studies have still to be tested in humans. When measuring the appetitive effects of drugs and drug cues, cognitive measures which reflect selective attention for salient stimuli (e.g. PPI of the startle reflex, LI, and EEG) may provide a more robust and reliable predictor of a person’s drug approach tendency than self-reported craving (see also). The present paper shows that motivational states can probably be measured indirectly by means of related cognitive functions such as attention. Measuring attentional bias may provide a fruitful approach to the assessment drug of motivation.

Conclusion
Studies on the cognitive processes involved in drug motivation and craving are scarce. More knowledge on human cognitive neuropharmacological processes of craving and drug approach is needed. The present cognitive approach to craving leads to numerous research questions. What is the nature and extent of the relationship between attentional bias, craving, and drug approach tendency? Is attentional bias an essential modulator of craving? Does attentional bias predict drug use and relapse? Is attentional bias the results of increased dopaminergic activity? Which corticostriatal brain area is essential for this increased dopaminergic activity? Is there something like an increased premorbid attentional bias for general positive incentives in subjects at risk for substance dependence disorders? In addition to
the relevance of the model for our fundamental understanding of craving and for the treatment of addiction, the model may contribute to improvements in the assessment of craving and drug approach tendency as precursors of continued drug use and relapse. These hypotheses need to be explored in human studies, in order to validate the presented model. Thus, research on cognitive aspects of the neuropsychopharmacology of addiction has just begun.

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