Published in final edited form as:
Addict Biol. 2009 January ; 14(1): 108–118. doi:10.1111/j.1369-1600.2008.00136.x.

"Identifying the neural circuitry of alcohol craving and relapse vulnerability"

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Summary

With no further intervention, relapse rates in detoxified alcoholics are high and usually exceed 80% of all detoxified patients. It has been suggested that stress and exposure to priming doses of alcohol and to alcohol-associated stimuli (cues) contribute to the relapse risk after detoxification. This article focuses on neuronal correlates of cue responses in detoxified alcoholics. Current brain imaging studies indicate that dysfunction of dopaminergic, glutamatergic, and opioidergic neurotransmission in the brain reward system (ventral striatum including the nucleus accumbens) can be associated with alcohol craving and functional brain activation in neuronal systems that process attentional relevant stimuli, reward expectancy and experience. Increased functional brain activation elicited by such alcohol-associated cues predicted an increased relapse risk, while high brain activity elicited by affectively positive stimuli may represent a protective factor and was correlated with a decreased prospective relapse risk. These findings are discussed with respect to psychotherapeutic and pharmacological treatment options.

Keywords

alcohol craving; functional magnetic resonance imaging; relapse; reward system; dopamine; opioids

Introduction

Without further intervention, detoxification alone does little to prevent subsequent relapse in alcoholics: in the placebo control groups of treatment studies, up to 85% of all patients relapse, even if treated as inpatients until complete remission of physical withdrawal symptoms (Boothby and Doering, 2005). It has been suggested that exposure to stress and to priming doses of alcohol can induce a relapse (Adinoff, 2004; Breese et al., 2005; Cooney, 1997). Another relevant mechanism contributing to the relapse risk is the exposure to stimuli (cues) that have regularly been associated with alcohol intake; such stimuli can become conditioned cues that elicit conditioned responses such as alcohol craving and consumption (Adinoff, 2004; Berridge and Robinson, 1998; Di Chiara and Bassareo, 2007; Everitt and Robbins 2005). Here we review the theoretical background and the results of neuroimaging studies that tried to identify 1) the neuronal networks activated by alcohol-associated versus control cues

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with functional magnetic resonance imaging, and 2) alterations in relevant neurotransmitter systems that are associated with cue-induced brain activation and craving for alcohol.

A learning theory of alcohol craving

Alcohol dependence and other drug addictions are characterized by criteria such as tolerance development, withdrawal symptoms, drug craving and reduced control of drug intake (American Psychiatric Association, 1994; World Health Organization, 1992). It has been suggested that the development of tolerance, i.e. neuroadaptation of the brain to chronically increased alcohol consumption, results in a new homeostatic balance, which is disturbed when drug or alcohol intake is suddenly interrupted during detoxification and thus results in clinically manifest withdrawal symptoms (Koob, 2003). For example, alcohols sedative effects are mediated by stimulation of GABAergic and inhibition of glutamatergic neurotransmission (Tsai et al., 1995; Krystal et al., 2006). During withdrawal, increased glutamatergic excitation and insufficient GABAergic inhibition may result in epileptic seizures and other withdrawal symptoms (Tsai et al., 1995; Krystal et al., 2006). Patients may relapse because they fear such aversive and dangerous withdrawal symptoms. However, why do patients relapse long after acute withdrawal symptoms have ceased?

One explanation refers to conditioned reactions elicited by conditioned cues, i.e. stimuli that have previously been associated with alcohol intake. In opiate addiction, studies in animals and humans demonstrated that heroin-associated environmental cues triggered conditioned reactions that counteract the expected drug effect (Wikler, 1948; Siegel et al., 1982): rodents, which always received the same dose of opiate in the same cage, displayed a rather high tolerance to this opiate effect. Yet when they received the same dose in a different cage, this conditioned counter-adaptive response did not occur and the animals died because of an overdose. On the other hand, if the animals did not receive the expected opiate dose after being exposed to the contextual cue (cage), they showed symptoms of opiate withdrawal. Therefore it was suggested that the cage served as a conditioned stimulus, which caused a counter-adaptive reaction - opposite to the drug effect – that balances the drug effect or leads to withdrawal symptoms in case the expected drug effect does not arrive (Siegel, 1975). Likewise in alcoholism, contextual cues that characterize situations in which alcohol intake and its associated sedative effects are expected may act as conditioned stimuli that trigger counter-adaptive alterations in neurotransmission such as increased glutamatergic and decreased GABAergic neurotransmission. Again, in the absence of alcohol intake, the resulting hyperexcitation may manifest as withdrawal symptoms and trigger relapse (Verheul et al., 1999). In such situations, patients may experience craving for alcohol motivated by the desire to relieve the unpleasant experience of conditioned withdrawal. Indeed, about one third of all alcoholics in a clinical setting described that their relapse was preceded by a sudden manifestation of withdrawal symptoms, which occurred long after acute detoxification and were often triggered by (previously) “typical” drinking situations (Heinz et al., 2003).

However, craving for alcohol may also be triggered by environmental stimuli that have been associated with the rewarding, subjectively pleasant effects of alcohol intake (Stewart et al., 1984; Verheul et al., 1999; Heinz et al., 2003). According to this theory, originally neutral stimuli can be associated with alcohol's positive effects, so that these stimuli become conditioned stimuli (CS), which are associated with the positive effects of alcohol intake as an unconditioned response (UCR). These conditioned stimuli can elicit craving for the positive effects of alcohol - even without the presence of alcohol – as a conditioned response (CR) (Figure 1). Such formerly neutral stimuli, which are now associated with alcohol's positive effects, can be external cues such as the context, i.e. the environment during former alcohol consumption, or cues associated directly with alcohol intake such as the sight or the smell of the favourite beverage. However, internal stimuli such as feelings of loneliness or memories

of conflict situations, which had previously been associated with alcohol intake, can also become conditioned cues that trigger craving for alcohol's positive effects (Drummond, 2000; Heinz et al., 2003; Verheul et al., 1999).

In the last decade, considerable progress has been made in the attempt to identify the basic neuronal mechanisms that underlie cue-induced alcohol craving. Animal experiments revealed that alcohol and drug associated cues activate dopamine and endorphin release in the medial prefrontal cortex and the ventral striatum including the nucleus accumbens, a core area of the brain reward system (Shalev et al., 2000; Dayas et al., 2007; Di Chiara, 2002). In alcoholism, the sight of the favourite beverage could either elicit conditioned withdrawal symptoms or conditioned craving for alcohol's positive effects and thus facilitate relapse (Heinz et al., 2003). Within the scope of this psychophysiological paradigm, conditioned reactions can be assessed on multiple levels. The levels of reactions differ conceptually and can be influenced by the conditioned cue with different intensity (Carter and Tiffany, 1999). In human studies, a now well-established method to investigate the described theoretical approaches is the combination of a “cue-reactivity” paradigm with functional magnetic resonance imaging (Braus et al., 2001; Drummond, 2000; George et al., 2001; Grüsser et al., 2004).

Empiric relation of craving and relapse

While animal studies strongly support the hypothesis that conditioned drug reactions are involved in the development and maintenance of addictive behaviour and relapse (Robbins and Everitt, 2002; Di Chiara, 2002; Robinson and Berridge, 1993), in alcohol-dependent patients the empiric connection between craving and the following relapse is far less clear. Several studies found *no* positive correlation between alcohol craving and relapse (Drummond and Glautier, 1994; Grüsser et al., 2004; Junghanns et al., 2005; Kiefer et al., 2005; Litt et al., 2000; Rohsenow et al., 1994), whilst other studies did observe such relationship (Bottlender and Soyka, 2004; Cooney et al., 1997; Heinz et al., 2005c; Ludwig and Wikler, 1974; Monti et al., 1990) (Table 1). In contrast to this, changes in physiological parameters elicited by alcohol-associated cues seem to be more closely connected to relapse (Abrams et al., 1988; Braus et al., 2001; Drummond and Glautier, 1994; Grüsser et al., 2004; Rohsenow et al., 1994).

Within cue-reactivity paradigms, the often low correlation between subjectively reported craving and the actual consumptive behaviour may be explained by divergent reactions to alcohol and alcohol-associated cues, which do not necessarily emerge on all levels (subjective, motor, physiological) at the same time. Tiffany (1990) described a cognitive model in which conscious craving only occurs if the automatic process of drug intake is interrupted, which may be triggered by conditioned stimuli and motivate for drug intake even in the absence of conscious drug urges. Inhomogeneous data concerning the association between craving and relapse could further be explained by the heterogeneous research methods, settings and samples during data collection. For example, it was shown that the psychological level (cue-induced craving) and the physiological level (enhanced drug-like arousal) were dissociated in abstaining alcoholics (Breese et al., 2005). Likewise in a study with cocaine-addicted patients, it was demonstrated that an effective psycho-social treatment with the aim to reduce drug craving helped patients to stay abstinent in spite of the persistence of subjectively high craving (Weiss et al., 2003). It has even been suggested that the conscious sensation of alcohol craving can serve as a warning sign that helps patients to get help and thus maintain abstinence (Drummond and Glautier, 1994; Monti et al., 1990). However, craving seems to lead to relapse if it occurs in stressful situations (Breese et al., 2005; Cooney et al., 1997).

Neurobiological correlates of alcohol craving

In drug and alcohol dependence, different neurotransmitter systems interact with different types of relapse situations (cue-, stress-, or priming-induced) (Shalev et al., 2000; Heinz et al., 2003). Specifically, it was suggested that the rewarding effects of alcohol and all other dugs of abuse are mediated by ethanol-induced dopamine release in the nucleus accumbens (Wise, 1988). In a seminal article, Robinson and Berridge (1993) differed between the subjectively pleasant, hedonic drug effect ("liking") and the craving for that positive effect ("wanting") and attributed these effects to different neurotransmitter systems. They suggested that the pleasure ("liking") during drug intake as well as during consumption of primary reinforcers such as food is caused by opioidergic neurotransmission in the ventral striatum including the nucleus accumbens (Berridge and Robinson, 1998). Berridge and Robinson (1998) also suggested that craving, i.e. the "wanting" or desire for the drug, is not necessarily accompanied by positive feelings. Based e.g. on the work of Schultz and coworkers (1997), they suggested that the neurobiological correlate of "wanting" is (phasic) dopamine release in the ventral striatum.

Schultz and others observed that the arrival of unexpected reward elicits a burst of spikes in dopaminergic neurons (Schultz et al., 1997). However, if this incident is predicted by a conditioned cue, the discharge of the dopaminergic neurons occurs directly after the presentation of this conditioned cue and reflects the magnitude of the anticipated reward (Tobler et al., 2005). However, when the reward itself arrives as expected (anticipated), it no longer elicits a dopamine discharge (Schultz et al., 1997) (Figure 2). Robinson and Berridge suggested that phasic dopamine release facilitates the allocation of attention towards salient, reward-indicating stimuli, which can motivate the individual to show a particular behaviour to get the reward.

Schultz and coworkers also showed that if the reward does not occur although it was anticipated after the presentation of a reward-indicating, conditioned cue, there is a transient cessation of dopamine neuron firing precisely after the moment when the expected reward does not arrive (Schultz et al., 1997) (Figure 2). Thus the dopaminergic system acts as an error-detection signal, which indicates the unexpected arrival of salient new stimuli and of surprising rewards as well as the non-expected reinforcers. Dopamine release in the nucleus accumbens in response to dopamine neuron firing thus encodes the expected magnitude of a potential reinforcer and therefore contributes to the control of goal directed behaviour. The nucleus accumbens may thus act as a "sensory motor gateway" (Tobler et al., 2005), which controls the effects of salient environmental stimuli on brain areas that regulate motor behaviour.

Striatal dopamine release is regulated by the hippocampus, which plays a major role in memory processes (Lisman and Grace, 2005). In rats that had formerly consumed cocaine, the stimulation of glutamatergic neurons in the hippocampus resulted in dopamine release in the ventral striatum and led to renewed drug intake (Vorel et al., 2001). Hippocampal stimulation may reflect real-life situations in which contextual, drug-associated cues activate the hippocampus and thus trigger memories associated with previous drug use (Figure 3). In this situation, hippocampal activation that leads to increases in dopamine neuron activity in the ventral tegmentum can elicit dopamine release in the ventral striatum, which facilitates drug intake (Floresco et al., 2001).

In detoxified alcoholics, brain imaging studies with positron emission tomography (PET) revealed a reduction of availability and sensitivity of central dopamine D2-receptors in alcohol-dependent patients, which may reflect a compensatory down-regulation after chronic alcohol intake and was associated with the subsequent relapse risk (Heinz et al., 1996; Volkow et al., 1996). Further PET studies showed that alcohol craving was specifically correlated with a low dopamine synthesis capacity measured with F-DOPA PET and with reduced dopamine D2

receptor availability in the ventral striatum including the nucleus accumbens (Heinz et al., 2005c; Heinz et al., 2004). During detoxification and early abstinence, dopamine dysfunction may further be augmented by reduced intra-synaptic dopamine release: animal experiments showed that extracellular dopamine concentrations decreased rapidly during detoxification (Rossetti et al., 1992) and a PET study showed that dopamine release following amphetamine administration was significantly reduced in detoxified alcoholics (Martinez et al., 2005). These studies indicate that after detoxification, overall dopaminergic neurotransmission in the ventral striatum of alcohol-dependent patients is reduced. Therefore, it is unlikely that in this situation, the presentation of alcohol-associated cues can cause a significant dopamine release that triggers reward craving or relapse. As a matter of fact, animal studies demonstrated that the presentation of alcohol and drug-associated cues can lead to relapse even if no dopamine is released in the ventral striatum (Shalev et al., 2002). However, as described above, dopamine dysfunction in human studies was correlated with the severity of alcohol craving and also with increased processing of alcohol-associated cues in the anterior cingulate and medial prefrontal cortex (Heinz et al., 2004), brain areas in which an increased processing of alcohol cues has been associated with an increased relapse risk (Grüsser et al., 2004). So how can dopamine dysfunction contribute to alcohol craving and cue reactivity? But before we try to answer this question, we should briefly discuss which other neurotransmitter systems may modulate cue reactivity and craving in alcoholism.

A long-term sensitisation towards the effects of drugs and drug-associated cues can be caused by structural changes in striatal GABAergic neurons, which are innervated by dopaminergic neurons and play a major role in the signal transfer towards the thalamus and the cortex (Robinson and Kolb, 1997). Alcohol stimulates GABA receptors and inhibits the function of glutamatergic NMDA-receptors (Kalivas and Volkow, 2005; Krystal et al., 2006). The alcohol-induced inhibition of the glutamatergic signal transduction results in up-regulation of NMDA receptors (Tsai et al., 1995; Schumann et al., 2005). Loss of alcohol-associated inhibition of NMDA receptor function may result in hyperexcitation and clinically manifest as withdrawal symptoms (Spanagel, 2003). Repeated withdrawals elicit enhanced glutamate release (Kalivas et al., 2005). It has been suggested that glutamatergic neurotransmission in pathways from the prefrontal cortex (PFC), amygdala and hippocampus to the nucleus accumbens and ventral tegmental area (VTA) plays a major role in triggering relapse (Kalivas et al., 2005). Therefore, modulation of NMDA-receptor e.g. by Acamprosate is a promising approach for pharmacological treatment of alcohol craving (Mann et al., 2004; Spanagel, 2003).

Alcohol seems to modulate NMDA receptors via interfering with a glycine binding site on the receptor (Tsai et al., 1995); in that context it is interesting to note that cue-induced relapse was influenced by a glycine binding antagonist but not by competitive nor not-competitive NMDA-receptor antagonists (Bachteler et al., 2005; Backstrom and Hyytia, 2004). Period- (Per-) genes regulate the circadian rhythm and influence glutamatergic neurotransmission. An interesting study found evidence that this gene affects alcohol intake in alcoholics (Spanagel et al., 2005) and in an animal model of excessive alcohol intake: Per2-(Brdm1-) mutant mice revealed an increased glutamate concentration in the suprachiasmatic nucleus and displayed enhanced alcohol intake. Acamprosate normalised glutamate levels and reduced the amount of consumed alcohol (Spanagel et al., 2005). To date, NMDA receptors cannot easily be visualized by PET. However, glutamate concentrations can be measured in vivo with spectroscopy (MRS), and first studies report correlations between glutamate concentrations in the hippocampus and theta oscillations in healthy controls (Gallinat et al., 2006), thus suggesting that MRS may be used to measure glutamate concentrations in association with cue reactivity in alcoholics.

Further neurotransmitter systems which are involved in the development and maintenance of alcohol craving are the cannabinoid and opioidergic system. There is a high concentration of CB1-receptors in the PFC, the amygdala, the VTA, the hippocampus, the nucleus accumbens

and the ventral striatum. CB1-receptors modulate the release of DA, GABA and glutamate and elicit long-term changes in synaptic transmission (”long-term potentiation“, LTP and ”long-term depression“, LTD) (De Vries and Schoffelmeer, 2005). The blockade of the CB1-receptors in animal models of excessive nicotine and methamphetamine consumption reduced the drug intake during relapse (De Vries and Schoffelmeer, 2005), and CB1 receptor stimulation in the PFC is required for the behavioural expression of cue-elicited fear conditioning (Laviolette et al., 2005).

Human alcoholics displayed an increase of μ-opiate receptors in the ventral striatum, which was correlated with the severity of alcohol craving (Heinz et al., 2005b). In alcohol-dependent patients, naltrexone blocked alcohol craving and the subjective “high”, i.e. drug “liking”, associated with alcohol intake (O'Brien, 2005). In animal experiments, blockade of μ-opiate receptors with naltrexone reduced dopamine release in the ventral striatum and alcohol intake (Gonzales and Weiss, 1998). In humans, several clinical studies showed that naltrexone treatment can reduce the relapse risk of alcoholics and lower the amount of consumed alcohol (Srisurapanont and Jarusuraisin, 2005; Streeton and Whelan G, 2001, but see Krystal et al., 2001), particularly if applied in patients with a potential high affinity, gain-of-function μ-opiate receptor genotype (Ray and Hutchinson, 2007; Oslin et al., 2003).

Functional imaging studies on cue-induced alcohol craving

Cue-induced functional brain activation can be indirectly assessed by measuring changes in cerebral blood flow with positron emission tomography (PET) or single photon emission computed tomography (SPECT) or by measuring the blood oxygen level dependent (BOLD) response with functional magnetic resonance tomography (fMRI). While these studies revealed considerable inter-individual variance in response to the presentation of alcohol-associated stimuli, there are some core regions which were activated in most studies (de Mendelssohn et al., 2004; Weiss, 2005). These core regions include:

- the *anterior cingulate (ACC)* and the adjacent *medial prefrontal cortex*, involved in attention-and memory processes, which encode the motivational value of stimuli (Grüsser et al., 2004; Heinz et al., 2004; Myrick et al., 2004; Tapert et al., 2004)
- the *orbitofrontal cortex (OFC)*, involved in evaluation of reward of stimuli (Myrick et al., 2004; Wrase et al., 2002)
- the *basolateral amygdala*, which specifies the emotional salience of stimuli and initiates conditioned and unconditioned approach and avoidance behaviour (Schneider et al., 2001)
- the *ventral striatum (including the nucleus accumbens)*, which connects motivational aspects of salient stimuli with motor reactions (Wrase et al., 2007; Braus et al., 2001; Wrase et al., 2002)
- the *dorsal striatum*, which consolidates stimulus-reaction-patterns and is involved in habit formation (Grüsser et al., 2004; Modell and Mountz, 1995)

The activation of other brain areas seems to depend upon the sensory quality of presented stimuli (e.g. activation of fusiform gyrus during visual, but not olfactory cues) (Braus et al., 2001) or the state of detoxification and alcohol availability (e.g. activation of the dorsolateral prefrontal cortex, which contributes to executive behaviour control, in acutely drinking patients who were given a priming dose of alcohol, George et al., 2001). However, results concerning the association between cue-induced activity in these brain areas and subjective craving for alcohol are not consistent. One study observed an association between the severity of craving and functional brain activation in the ventral striatum, OFC and ACC (Myrick et al., 2004), another one in the dorsal striatum (Modell and Mountz, 1995), a third in the subcallosal gyrus

(Tapert et al., 2004) and some other studies observed no significant correlation between alcohol craving and brain activation (Grüsser et al., 2004; Heinz et al., 2004) (Table 2). A reason for these disparate findings could be the diverse nature of the stimuli used in the different studies: some studies used alcohol related words (Tapert et al., 2004) and others alcohol related pictures, either with (Myrick et al., 2004) or without (Grüsser et al., 2004) a sip of alcohol ("priming dose"). Moreover, in some studies patients were not detoxified and thus able to consume larger amounts of alcohol, at least to a later time point (Myrick et al., 2004), while in other studies the patients were detoxified and participated in an inpatient treatment program, where relapse would cause termination of treatment (Braus et al., 2001; Grüsser et al., 2004; Heinz et al., 2004; Heinz et al., 2007; Wrase et al., 2002; Wrase et al., 2007). The above mentioned difficulties to assess subjective craving may also contribute to these inconsistencies.

Imaging studies on the prospective relapse risk

While a multitude of studies investigated brain activation during the presentation of alcohol-associated stimuli, only a very few studies assessed to what extent brain activation elicited by alcohol or affective cues predicts an increased relapse risk in the further course of treatment. In a pilot study with alcohol-dependent patients, alcohol cues elicited increased activation of visual association centres and the ventral striatum in detoxified alcoholics compared to control subjects (Braus et al., 2001). Furthermore, patients who suffered from multiple relapses during their previous course of disease and relapsed rather quickly after detoxification showed a stronger cue-induced activation of the ventral striatum than patients who previously managed to abstain from alcohol for longer periods of time and who also managed to abstain during the six-month follow-up period. Grüsser et al. (2004) were able to replicate these findings in another study, again with a rather small sample size: subsequently relapsing patients displayed an increased BOLD response elicited by alcohol-associated stimuli in the anterior cingulate and adjacent medial prefrontal cortex and the central (dorsal) striatum. These observations are in the line with animal experiments in which cue-induced relapse after cocaine consumption was prevented by blockade of dopamine and AMPA glutamate receptors in the *dorsal* striatum (Vanderschuren et al., 2005). It has been suggested that the dorsal striatum is crucial for habit learning, i.e. for the learning of automated responses, and may thus contribute to the compulsive character of dependent behaviour. On the other hand, in addicted individuals, cue-elicited craving tends to preferentially elicit dopamine release in more dorsal striatal structures, which is thought to reflect a transition from a ventral striatal reward-driven phenomenon to a dorsal striatal stimulus-response habit formation (Berke and Hyman, 2000), in which reward plays a lesser role. Indeed, Robbins and Everitt have proposed that although the initial reinforcing effects of drugs of abuse may activate the ventral striatum, when the drug taking transitions into habitual drug-seeking behaviors, activation of the more dorsal striatal regions predominate (Robbins and Everitt, 2002). Thus, although cue-elicited craving will activate ventral striatal structures in terms of glucose metabolism, in addicted individuals the cues tend to preferentially release dopamine in the dorsal striatum and putamen (Volkow et al., 2006; Wong et al., 2006).

Also, in our clinical experience, many patients describe their relapse in terms of such automated actions and do not remember to have experienced craving before the relapse occurred (Tiffany, 1990). In a recent study, alcohol cues were not presented in a block design for 20 seconds as in the studies of Braus et al. and Grüsser et al. (Braus et al., 2001; Grüsser et al., 2004) but instead were presented only for 750 ms in a single event design (Heinz et al., 2007). The briefly presented alcohol pictures elicited increased brain activation in alcoholics versus controls in the prefrontal and cingulate cortex, however, no significant correlation with the subsequent relapse risk was observed. Sample size limitations or differences in brain activation depending on the duration of stimulus presentation may contribute to these differences. However, increased brain activation elicited by positive versus neutral stimuli in the ventral striatum was

correlated with a subsequently *reduced* relapse risk. If independently replicated, increased responses to affectively pleasant stimuli may represent a protective factor that could potentially be targeted by psychotherapy.

Besides increased responses to alcohol-associated cues in brain areas associated with motivation and affect, dysfunction of brain areas associated with executive behaviour control may also contribute to the relapse risk. Indeed, one study in methamphetamine-dependent patients showed that subsequent relapse was predicted by activation patterns elicited during a two-choice decision-making task in the insula, posterior cingulate and temporal cortex (Paulus et al., 2005). However, so far this hypothesis has not been tested in alcohol-dependent patients.

Neurotransmitter dysfunction and cue reactivity

So far, only a few studies directly examined the correlation between cue-induced brain activation and dopamine dysfunction in alcoholics. To date, no study assessed the correlation between cue-induced brain activation and other neurotransmitter systems such as glutamate or GABA in alcoholics. In recently detoxified alcohol-dependent patients, the prospective risk of relapse was associated with the extent of alcohol craving, which in turn was correlated with both a low dopamine synthesis capacity measured with F-DOPA PET and with a reduced availability of dopamine D2-receptors in the ventral striatum (Heinz et al., 2005c; Heinz et al., 2004). The reduction of dopamine D2-receptors in the ventral striatum was correlated with increased fMRI activation of the anterior cingulate and adjacent medial prefrontal cortex during the presentation of alcohol-associated versus neutral control cues (Heinz et al., 2004). These brain areas have been associated with attribution of attention to salient stimuli (Fuster et al., 1997). But why would alcohol-associated stimuli elicit brain activation in the attention network, if they are presented in a setting that does not offer any chance to obtain alcohol, i.e. in a loud and noisy scanner to patients who are in a detoxification program that excludes any alcohol use?

The work of Schultz et al. (1997) showed that phasic alterations in dopamine release are not only required to learn new stimulus-reward associations but also that they may be necessary to unlearn established associations: a phasic dip of dopamine release occurred whenever a conditioned stimulus is not followed by the anticipated reward (Figure 2). It has been suggested that dopamine dysfunction during early abstinence, i.e. low dopamine synthesis, reduced stimulus-induced dopamine release and D2 receptor availability in the ventral striatum of detoxified alcoholics (Heinz et al., 2005c; Heinz et al., 2004; Martinez et al., 2005) may interfere with this dopamine-dependent signalling of an error in reward expectation (Heinz et al., 2004). Therefore, it may be difficult for alcoholics to divert attention away from conditioned cues, which have well been learned to signal the availability of alcohol (maybe via glutamate-dependent long-term potentiation of the ventral hippocampus-ventral striatal pathway that has been associated with perseverative behaviour; Goto and Grace, 2005), if dopamine dysfunction interferes with the phasic dopamine-dependent error signal indicating that alcohol-associated cues are no longer followed by reward. Indeed, a linear correlation was found between alcohol cue-induced activation of the medial prefrontal cortex and the reduction of dopamine D2 receptor availability in the ventral striatum of detoxified alcoholics, suggesting that the degree of dopamine dysfunction contributes to excessive salience attribution to alcohol-associated cues (Heinz et al., 2004). Maybe that is why in our clinical experience, many detoxified alcohol-dependent patients report difficulty to remaining abstinent when confronted with alcohol advertisements in typical drinking situations (e.g. when sitting alone at home and watching a football game); unfortunately, there are no studies about the impact of alcohol ads on the relapse risk of alcoholics.

If dopamine dysfunction in detoxified alcoholics interferes with phasic changes in dopaminergic neurotransmission, alcohol-dependent patients should also have problems in attributing salience to newly learned conditioned stimuli, which are presented unexpectedly and indicate the availability of reward. Indeed, a reduced functional activation of the ventral striatum was found in alcoholics who were confronted with cues that indicated the availability of reward (Wrase et al., 2007). This reduced activation of the ventral striatum correlated with the severity of alcohol craving and was not explained by differences in performance or mood between alcoholics and control subjects. Reduced brain activation to new reward-indicating stimuli may thus interfere with the patients' motivation to experience new and potentially rewarding situations. Moreover, the same patients displayed an increased activation of the ventral striatum when confronted with alcohol-associated stimuli, which was also correlated with the severity of alcohol craving. This finding is in accordance with the hypothesis that alcohol and other drugs of abuse “hijack” a dysfunctional reward system, which tends to respond too strongly to drug-associated cues while failing to adequately process conventional, primary reinforcers such as food or sex (Volkow et al., 2004). More specifically, within the framework of the studies of Schultz et al. (1997), these findings may help to explain why it can be difficult to motivate detoxified alcoholics to replace alcohol by other reinforcers such as social interactions or new hobbies: their neuronal responses to new reward-indicating stimuli are reduced, while those to alcohol-associated cues are increased, which may make it very difficult to divert attention from alcohol-associated cues signalling the availability of alcohol and its dopamine-stimulating pharmacological effects (Di Chiara, 2002; Di Chiara et al., 2007).

Therapeutical consequences

The presented data suggest different therapeutic consequences. First of all, functional imaging studies can help to identify patients who are particularly at risk to suffer a relapse as a result of increased reactions to alcohol-associated cues. Since imaging techniques such as fMRI are currently too expensive, the employment of less complicated techniques that assess physiological responses to alcohol cues such as the affect-modulated startle response (Heinz et al., 2003) are of particular clinical relevance. Many alcohol-dependent patients deny alcohol craving during the presentation of alcohol-associated pictures, but they show strong appetitive reactions to alcohol cues when assessed with the startle response (Heinz et al., 2003). Secondly, specific psychotherapeutic methods may be developed for alcohol-dependent patients with strong cue reactivity and a high risk for relapse. For example, treatments using cue exposure have repeatedly been investigated in therapeutic studies, however, so far they do not seem to yield significantly better results than standard therapy with cognitive-behavioural and supporting interventions (Kavanagh et al., 2004; Löber et al., 2006). However, this treatment may be specifically successful in patients who show strong cue reactivity. Therefore, identification of patients with strong neuronal responses to alcohol cues may provide an opportunity to successfully treat this subgroup of patients with cue exposure therapy. Thirdly, the results of this review suggest that an effective strategy may involve testing of the effects of additive pharmacotherapy on cue-induced neuronal activation patterns. One pilot study showed that alcohol cue-induced activation of the thalamus is blocked by acute application of amisulpride in detoxified alcoholics (Hermann et al., 2006), however, chronic effects on alcohol intake and the relapse risk remain to be explored.

Summary and outlook

Current research about the different neurobiological mechanisms of relapse raises hope for a therapy of alcohol dependence that is adapted to individual relapse mechanisms and needs. Furthermore, neuroscientific research can contribute to the reduction of the stigmata of addiction. In contrast to common assumptions that prevailed until the second half of the 20th

century, relapse in alcohol-dependent patients does not seem to reflect “bad intentions” or “weak willpower”. Rather, in vivo imaging studies point to an increased sensitivity of brain areas to alcohol-associated stimuli, which may be in part genetically influenced (Heinz et al., 2005a). Cue-induced brain activation predicted the relapse risk of alcohol-dependent patients better than conscious craving, which is not surprising given that activation of some brain areas such as the striatum is hardly associated with conscious experiences. Therefore, it seems plausible that patients often relapse “against their own [conscious] will” and they should be treated with the same respect as any other patient in the health care system.

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FIGURE 1.
Model of conditioned alcohol craving: a previously neutral stimulus, which has been regularly associated with alcohol consumption (for example the view of a beer glass), can become a conditioned stimulus that is able to elicit alcohol craving.

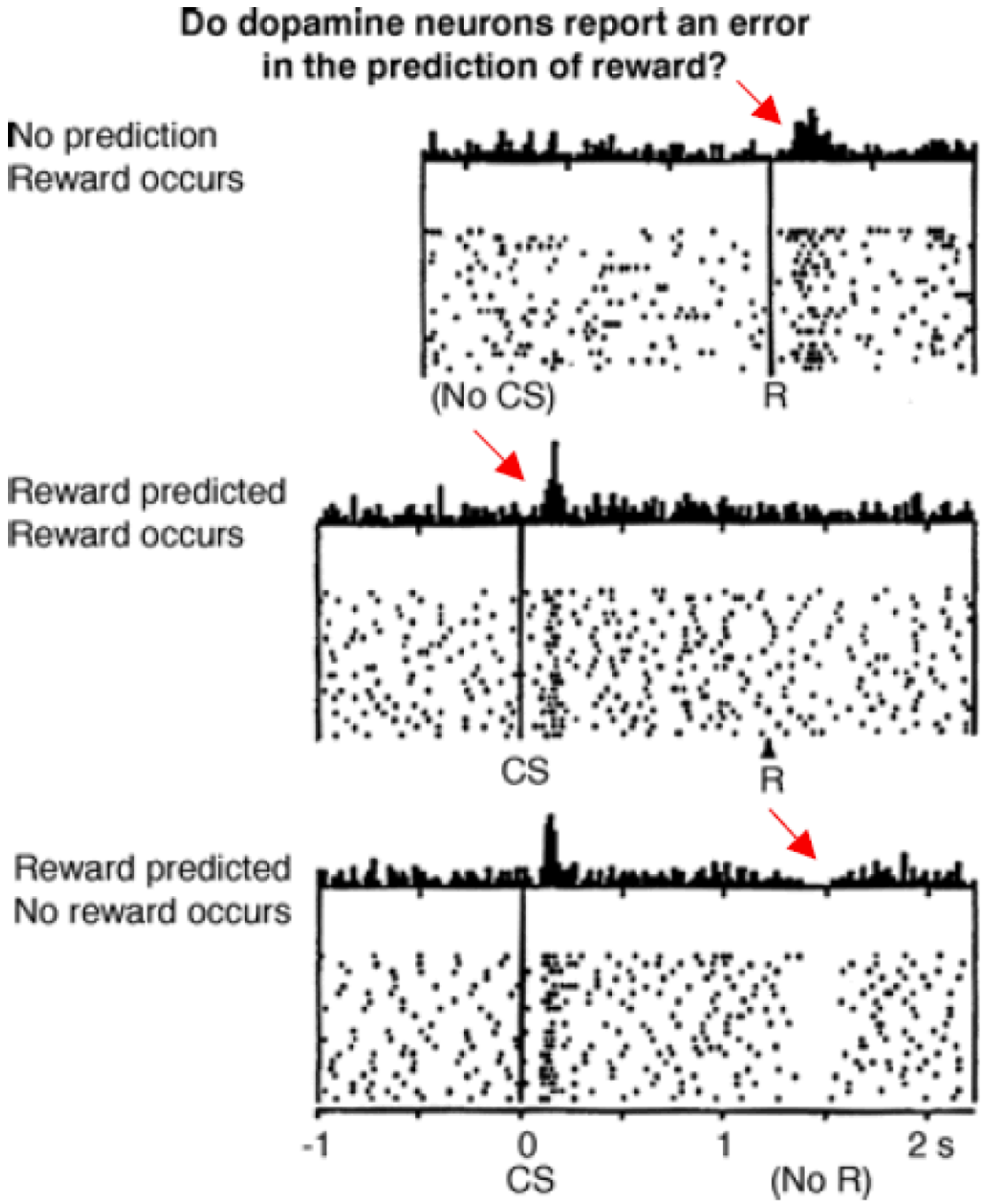

FIGURE 2.

Reward-associated error signalling by short-term ("phasic") dopamine release (cf. Schulz et al., 1997). Top: An unexpected reward (banana pallets for rhesus monkeys), which was not predicted by previous stimuli, generates an error in reward prediction (unexpected reward) that is reflected in a short term increase in dopamine firing. Middle: After learning that a previously neutral (now conditioned) stimulus (light) regularly predicts a reward, the surprising appearance of the conditioned stimulus reflects an error in reward prediction and generates a short-term increase in phasic dopamine firing rate. The reward itself is now completely predicted by the conditioned stimulus and does not elicit dopamine firing. Bottom: If a

conditioned stimulus is not followed by the expected reward, an error in reward prediction occurs (unexpected lack of reward), which is reflected in a phasic decrease in dopamine firing.

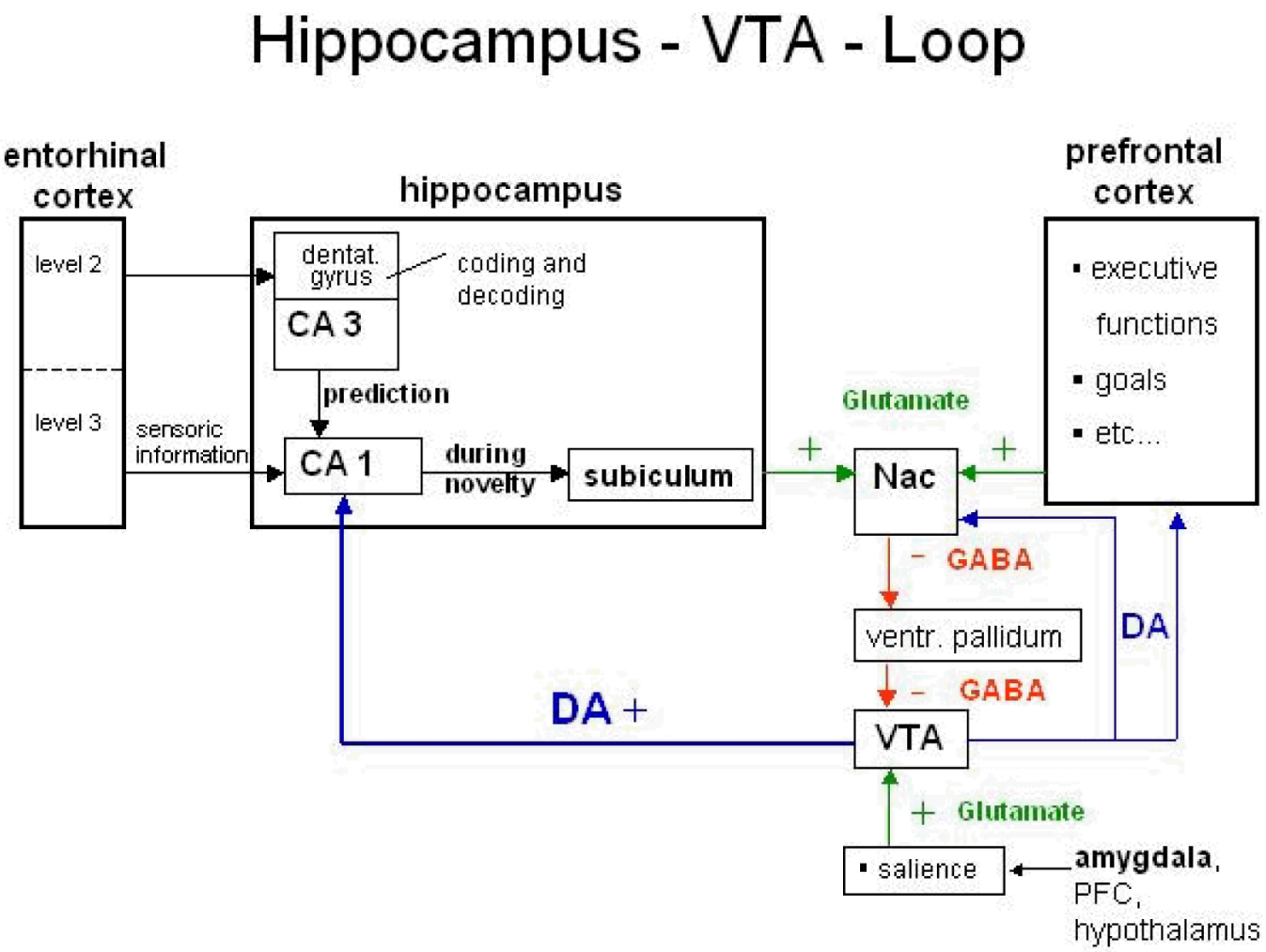

FIGURE 3.

Model of a neuronal network that includes dopamine-related prediction of unexpected or novel reward and reward-associated stimuli: the discrepancy between expected and actual sensory informations is calculated in the hippocampus (CA1) and activates dopaminergic neurons in the brainsteam (VTA) via glutamatergic projections to the nucleus accumbens (ventral striatum). The VTA in turn modulates neuronal transmission in CA1 via an increased dopamine-release in the hippocampus and thus contributes to memory performance. The prefrontal cortex contributes to executive control functions and modulates - just as the limbic system - the firing rate of dopaminergic neurons that project from the brainsteam (VTA) to the nucleus accumbens (modified referring to Lisman and Grace, 2005).

Table 1

Correlation between subjective alcohol craving and physiological cue-induced reactions on the one side and relapse on the other side.

Subjective craving	**Physiological reactions**
Correlation with relapse	
Ludwig et al., 1974	Abrams et al., 1998
Monti et al., 1990	Rohsenow et al., 1994
Cooney et al., 1997	Drummond and Glautier, 1994
Bottlender and Soyka, 2004	Braus et al., 2001
Heinz et al., 2005	Grüsser et al., 2004
No correlationwith relapse	
Drummond and Glautier, 1994	
Rohsenow et al., 1994	
Litt et al., 2000	
Grüsser et al., 2004	
Junghanns et al., 2005	
Kiefer et al.,2005	

Table 2

Responsive brain activity to alcohol stimuli within adult alcohol-dependent patients vs. healthy controls

authors	[*n*]	Activation to alcohol vs. neutral stimuli	regions
Myrick et al., 2004	10 patients	pictures	bi insula
			medial anterior cingulate
fMRI	10 controls		bi ventral striatum
			r VTA
		correlation between alcohol pictures and craving	l ventral Striatum
			l orbitofrontal cortex (OFC)
			l anterior cingulate (ACC)
Tapert et al., 2004	8 female patients	words	l subcallosal gyrus
			l ACC
fMRI	9 controls		l DLPFC
			l OFC
			bi insula
			bi uncus
		correlation between alcohol words and craving	l subcallosal gyrus
Grüsser et al., 2004	10 patients	pictures	bi ACC
			l medial and superior PFC
FMRI	10 controls		bi dorsal striatum
			bi secondary visual areas
		correlation between alcohol pictures and craving	no significant activation
		association of alcohol pictures and relapse	medial ACC/medial PFC
			bi dorsal striatum
Wrase et al., 2002	6 patients	pictures	bi ventral striatum
			bi OFC
fMRI			bi thalamus
			bi ACC
			bi parietal lobe
			bi DLPFC
			bi fusiform gyrus
			bi occipital lobe
Braus et al., 2001	4 patients	pictures	bi ventral striatum
	4 controls		l fusiform gyrus
		after 3 weeks of treatment	l fusiform gyrus
Schneider et al., 2001	10 patients	smell	r amygdala

authors	**[*n*]**	**Activation to alcohol vs. neutral stimuli**	**regions**
			l cerebellum
fMRI	10 controls	after 3 weeks of treatment	r insula
			r occipital cortex
George et al., 2001	10 patients	pictures	medial thalamus
fMRI	10 controls		l medial frontal gyrus
Modell and Mountz, 1995	9 patients	Imagination of pleasant drinking experiences + smell and sip of favourite alcoholic drink	r dorsal striatum
SPECT	no controls	Correlation with craving	r dorsal striatum