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Neurobiology of substance-related addiction: findings of neuroimaging

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1. From consumption to addiction: understanding the course of disease

Current research on alcohol and drug dependence gradually showed that the development of addiction has to be understood as a complex interplay of psychological factors and neurobiological adaptation processes induced by consumption-related behavioural changes. Therefore, we review the results of recent neuroimaging research in humans that tried to understand the development of drug addiction in each of its stages. After giving an introduction to the imaging techniques and to the main neuroanatomical and –chemical targets of addiction research, we review changes in the brains' neuronal networks and in relevant neurotransmitter systems related to the processing of substance-related stimuli. We continue by reporting alterations in attention networks and memory formation, which are considered to be relevant for sustaining drug intake. We proceed by outlining imaging results on phenomena which are considered to define addiction itself like craving and withdrawal. Finally, we give an overview on neuroimaging research on relapse risk. We conclude with some comments on possible therapeutical implications of recent imaging results and on future perspectives.

1.1 Methodological approaches

Technical improvement in the neurosciences has provided powerful tools for research on functional brain activity related to addictive behaviour in humans. There are different imaging techniques which are most commonly used during the last decade. Since the neuroscientific methods used also give us information about scientific questions which could not yet be answered, the available imaging methods will shortly be addressed from a methodological point of view.

One way to understand the brains' functional organisation is using the functional Magnetic Resonance Imaging (fMRI) technique. This method allows for indirectly assessing neuronal activity by measuring changes in local blood flow. In detail, it measures the ratio of oxygenated and des-oxygenated blood, the so called blood oxygen level dependent (BOLD) contrast. This allows for an estimation of the underlying neural activity, since it has been shown that changes in blood flow and blood oxygenation are linked to neuronal activity (Kwong et al., 1992; Logothetis, 2002; Ogawa et al., 1990). fMRI is one of the most prominent

neuroimaging techniques because of its non-invasiveness, the lack of radiation exposure, the relatively high availability and its good spatial resolution. Disadvantages of the method are the rather poor temporal resolution (e.g. versus EEG), the lack of an absolute baseline of activity and the fact that specific neurotransmitter systems can not be systematically assessed without applying specific agonists/ antagonists.

In contrast to fMRI, the so called Positron Emission Tomography (PET) as well as Single Photon Emission Computed Tomography (SPECT) allow for measurement of an absolute baseline of activation. Furthermore, these imaging methods can quantify neuroreceptor and transporter availabilities, although a potential confound of endogenous neurotransmitter concentration competing for binding of receptors/ transporters with radioligands has to be taken into account (Heinz et al., 2004a; Kumakura et al., 2007; Laruelle 2000).

Clear disadvantages of PET and SPECT measurements are the application of a radioactive contrast agent exposing the subject to gamma radiation, the often rather short half-life period of the commonly used tracers and the rather high expenses required.

An elegant way to link specific brain functions with certain neurotransmitter systems, like linking dopamine with the brain reward system, is to use the combination of both methods: the correlation of neuronal activation measured with fMRI and functions of neurotransmitter system measured with PET or SPECT, e.g. dopamine receptor D_2 availability or dopamine synthesis rate (Kienast et al., 2008).

1.2 Neuroanatomical core structures

Considerable progress has been made during the last two decades in the attempt to identify the basic neuronal mechanisms that underlie addictive behaviour. Animal studies 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 brains' reward system (Dayas et al., 2007; Di Chiara, 2002; Shalev et al., 2000). As already mentioned, functional brain activity related to addictive behaviour in humans can be indirectly assessed by measuring changes in cerebral blood flow with PET, SPECT or by measuring the BOLD response with fMRI. These neuroscientific techniques gain insight into the neurobiology of addiction when combined with paradigms, which are designed to study single components of addiction and its development, e.g. so-called "cue-reactivity" paradigms (e.g. Braus et al., 2001; Drummond, 2000; George et al., 2001; Grüsser et al., 2004). As it might be expected, studies reveal differing results regarding the main neuroanatomical regions of interest, depending e.g. on the specific paradigm used and on inter-individual differences in the functional neuroanatomy related to addiction. Nevertheless, there are some core regions in the brain which are repeatedly activated by drug-specific stimuli across studies: 1. The anterior cingulate cortex (ACC) and the adjacent medial prefrontal cortex. This brain region is considered to be involved in processes encoding the motivational value of a stimulus. Therefore, it is also of importance for attention and memory processes (Grüsser et al., 2004; Heinz et al., 2004b; Myrick et al., 2004; Tapert et al., 2004). 2. The orbitofrontal cortex (OFC). This brain area has been related to the evaluation of the reward value of processed stimuli (Myrick et al., 2004; Wrase et al., 2002). 3. The amygdala, mainly the basolateral part. The amygdala is known to represent the emotional salience of stimuli and it is involved in unconditioned and conditioned approach and avoidance behaviour (Schneider et al., 2001). 4. The ventral striatum including the nucleus accumbens. These brain regions are considered to code the motivational aspects of salient stimuli and to link

with motor reactions (Wrase et al., 2007; Braus et al., 2001; Wrase et al., 2002). 5. The dorsal striatum. It has been implicated in habit formation and the consolidation of stimulus-reaction-patterns (Grüsser et al., 2004; Modell & Mountz, 1995). 6. The dorsolateral prefrontal cortex (DLPFC). It contributes to the executive control of behaviour and might therefore be relevant for resisting craving for the substance of abuse (George et al., 2001) and to guide behavioural adaptation and learning (Park et al., 2010).

1.3 Relevant neurotransmitter systems

Beside the main neuroanatomical correlates of the development of alcohol and drug addiction, modern imaging methods like PET provide a powerful tool for the systematic examination of the underlying neurotransmitter systems and their changes. The first relevant neurotransmitter to mention in the context of the development of addiction is dopamine. All drugs of abuse are known to release dopamine, which reinforces drug-taking behaviour (Di Chiara & Bassareo, 2007) and chronically induces counter-adaptive processes such as receptor down-regulation (Koob, 2003). To give an example, PET studies in detoxified alcoholic showed a reduction of availability and sensitivity of central dopamine D_2-receptors, which can serve as an example of a neuroadaptive process after chronic alcohol consumption, which was further associated with the subsequent relapse risk (Heinz et al., 1996; Volkow et al., 1996).

A different mechanism is implicated by sensitisation: Neuroadaptation in terms of long-term sensitisation towards the effects of drugs and drug-associated stimuli 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 & Kolb, 1997). Drugs like alcohol also appear to directly stimulate GABA receptors and inhibits the function of glutamatergic NMDA-receptors (Kalivas & Volkow, 2005; Krystal et al., 2006).

The cannabinoid and opioidergic system are other neurotransmitter systems, which are involved in the development and maintenance of drug abuse. High concentrations of CB1-receptors are found in the prefrontal cortex, the ventral tegmental area, the amygdala, the hippocampus, and the ventral striatum including the nucleus accumbens, i.e. structures which are known to be of high relevance for addiction development. Further, CB1-receptors modulate the release of dopamine, GABA and glutamate and elicit long-term changes in synaptic neurotransmission, like long-term potentiation or depression (De Vries & Schoffelmeer, 2005), which may play a role in addiction-specific neuroadaptations.

2. Learning to maintain consumption

Brain-imaging studies have increasingly focused on the early phase of disease, i.e. researchers are more and more interested in identifying addiction-specific risk factors as well as in describing the initial behavioural processes and the resulting neuronal changes. Therefore, current imaging studies try to identify the neuronal correlates of learning processes including classical Pavlovian and instrumental conditioning involved in disease development as well as in the risk of relapse. On the one hand, the goal of such studies is to provide insight into the neurobiology of drug addiction and therefore to improve understanding of the brain. On the other hand, researches intend to provide new options for

specific behavioural interventions or psychopharmacological modification of alcohol craving and the risk of relapse.

2.1 Contextual cues

One important factor in the development of addiction is the occurrence of conditioned reactions elicited by conditioned cues, i.e. stimuli that have previously been associated with alcohol or drug consumption. For example, if an originally neutral stimulus (UCS), like a drinking glass, has been regularly associated with the consumption of a substance of abuse, like wine or other alcoholic beverages, the stimulus will also be associated with the positively experienced effects of alcohol as an unconditioned response (UCR) and turns into a conditioned stimulus (CS). As a consequence, this stimulus can itself provoke consumption or associated behavior as a conditioned response (CR; see Figure 1).

Conditioned alcohol craving

drinking glass ➡ (wine) ➡ relaxing effect ➡ craving ➡ relapse

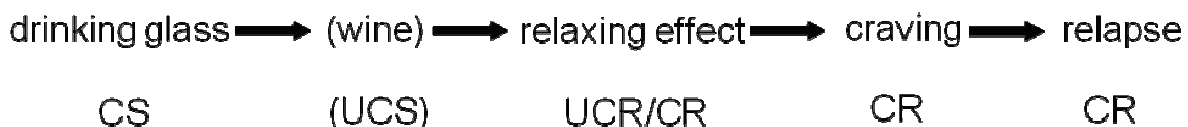CS   (UCS)   UCR/CR   CR   CR

Fig. 1. Model of conditioned alcohol consumption: a previously unconditioned stimulus (UCS; e.g. wine glass) is regularly associated with alcohol consumption. Thus, it becomes associated with the alcohol effect as an unconditioned response (UCR) and changes to a conditioned stimulus (CS). The CS itself is then able to elicit alcohol craving and even relapse as a conditioned response (CR).

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., 1975, 1982). Rodents which received opiate always in the same cage showed a rather high tolerance to the opiate effects until they received the same dose in a different cage. In the latter case, the conditioned counter-adaptive response did not occur and the animals died of an overdose of opiate. On the other hand, the animals showed symptoms of opiate withdrawal if they did not receive the expected opiate dose after being exposed to the contextual cue, i.e. the habitual cage. Likewise in humans, cues characterizing situations of alcohol or drug intake and their associated effects may act as conditioned stimuli that trigger counter-adaptive alterations in neurotransmission. Such changes may manifest as subjectively aversive withdrawal symptoms and lead to repeated drug intake, i.e. trigger relapse (Verheul et al., 1999).

2.2 Reward-associated changes in salience

If a person is repeatedly exposed to a drug or alcohol intake, different neuroadaptive changes are considered to happen. One important aspect is that our brains' attentional network is highly effective in learning to react to contextual or internal stimuli which are of high relevance, i.e. of high salience. Robinson and Berridge (1993) 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 achieve the

reward. With that assumption they referred to a fundamental work by Schultz and colleagues, who had observed that the occurrence of unexpected rewarding stimuli elicits a burst of spikes in dopaminergic neurons (Schultz et al., 1997). In contrast, if its appearance is signaled by a conditioned cue, the discharge of the dopaminergic neurons occurs already with the perception of the conditioned cue, and the rewarding stimulus itself does no longer elicit a discharge of dopamine. These results were remarkable, as Schultz and coworkers also showed that the absence of an expected reward after the occurrence of a conditioned cue leads to a transient cessation of dopamine neuron firing directly after the moment when the expected reward does not arrive (see Figure 2). Thus, the dopaminergic system indicates unexpected reward as well as the non-appearance of expected reinforcers, i.e. it serves as an error-detection signal and therefore contributes to learning, goal directed behaviour as well as behavioural flexibility. Furthermore, the dopamine signal reflects the magnitude of the anticipated reward (Tobler et al., 2005). Thus, the nucleus accumbens may act as a "sensory motor gateway" controlling the effects of salient contextual stimuli on prefrontal brain areas and limbic regions which regulate attention as well as motor behaviour.
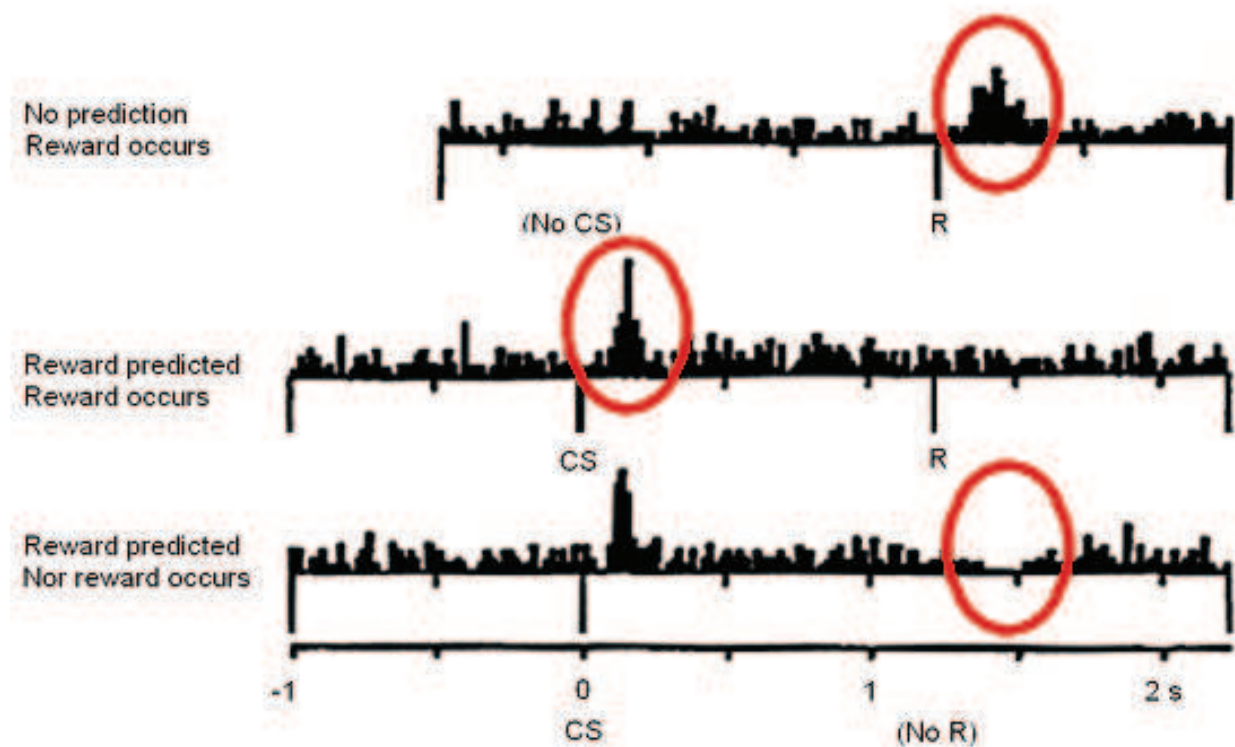

Fig. 2. Reward-associated phasic dopamine release (Schulz et al., 1997). *Top*: Unexpected and unpredicted reward (banana pellets for rhesus monkeys) is reflected in a short term increase in dopamine firing. *Middle*: After having learned that a light (conditioned stimulus, CS) regularly predicts a reward (R), the appearance of the CS generates a short-term increase in phasic dopamine firing rate. The reward itself is now completely predicted by the CS and does not elicit dopamine firing. *Bottom*: If a CS 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.

In humans, few studies directly examined the correlation between cue-induced brain activation and dopamine dysfunction or changes in other neurotransmitter systems such as glutamate or GABA. Studies showed that in detoxified alcohol-dependent patients, the extent of alcohol craving was correlated with both a low dopamine synthesis capacity measured with F-DOPA PET and with a reduced availability of dopamine D_2-receptors in the ventral striatum (Heinz et al., 2005b; Heinz et al., 2004b). This reduction was correlated with an increased activation of the anterior cingulate and adjacent medial prefrontal cortex measured with fMRI during the processing of alcohol-related versus neutral control stimuli (Heinz et al., 2004b). Interestingly, these brain areas have been associated with attention attribution to salient stimuli (Fuster et al., 1997). It seems surprising that alcohol-associated stimuli should provoke an increase in brain activation in attention network although all other contextual cues, in this case a loud and noisy MRI scanner, indicate that there is no chance for obtaining alcohol. One possible explanation is based on the work of Schultz and colleagues (1997) who demonstrated 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. In this phase of dependence, low dopamine synthesis, reduced stimulus-induced dopamine release and diminished D_2-receptor availability in the ventral striatum (Heinz et al., 2005b; Heinz et al., 2004b; Martinez et al., 2005) may interfere with dopamine-dependent processing of errors in reward expectation (Heinz et al., 2004b). Moving attention away from drug-associated conditioned stimuli and diminishing the attributed salience of such cues might be of specific difficulty for drug-dependent patients. Signaling of the potential availability of alcohol or the drug of abuse has been well learned, for example via glutamate-dependent long-term potentiation within the ventral hippocampus-ventral striatal pathway which has been associated with perseverative behaviour (Goto & Grace, 2005). In accordance with this hypothesis, a linear correlation between increased alcohol cue-induced activation of the medial prefrontal cortex and the reduction of dopamine D_2-receptor availability in the ventral striatum was found in detoxified alcoholics, further underlining that the degree of dopamine dysfunction may contribute to excessive salience attribution to alcohol-associated cues (Heinz et al., 2004b). Also in clinical experience, many detoxified alcohol-dependent patients report difficulty to remain abstinent when being confronted with scenes which still are of high salience for drug intake, i.e. typical drinking situations like someone sitting lonely on the sofa and watching TV ads for an alcoholic beverage.

Moving one step further, first studies indicate why the process of re-learning non-addictive behaviour seems so difficult to initiate: due to the described changes within the phasic characteristics of dopaminergic neurotransmission, alcohol-dependent patients may have problems in attributing salience to newly learned conditioned stimuli indicating the availability of non-drug reward. Wrase and colleagues (2007) observed a reduction in functional activation in the ventral striatum when being confronted with non-drug-associated, reward-indicating cues in alcoholics. Moreover, the reduced activation was correlated with the severity of alcohol craving and could not be explained by performance differences or mood. Reduced activation of the striatum to new, reward-indicating stimuli might therefore reflect the patients' diminished motivation to experience new and potentially rewarding situations. Interestingly, the same patients showed an increased activity of the ventral striatum when being confronted with alcohol-associated stimuli, which was also correlated with the severity of alcohol craving. Such a finding is in line with

the prominent hypothesis that substances of abuse "hijack" the reward system and stabilize a dysfunctional state, i.e. when the ventrial striatum primarily responds to drug-associated stimuli while the adequate processing of conventional, primary reinforcing stimuli such as food or sex is impeded (Volkow et al., 2004). Further research is needed to elucidate neuronal processing of natural reinforcers in addiction as well as (reversal) learning in general. For clinical practice, these findings also improve our understanding why it can be difficult to motivate detoxified alcoholics to replace alcohol by other reinforcers such as social interactions or new activities: their brains' response to alternative reward-indicating stimuli tends to be reduced in relevant brain regions. This may make it very difficult to - literally spoken - concentrate oneself on other aspects of the world than cues associated with the drug of abuse.

2.3 Modification in emotional response

One milestone of neurobiological research on alcohol and drug addiction is the observation that alcohol and all other drugs of abuse induce dopamine release in the ventral striatum, including the nucleus accumbens, and thus reinforce drug intake (Wise, 1988). Although a drug thus "reinforces" a specific behaviour, this does not necessarily imply that the drug effect is also subjectively pleasant. In a commonly known work by Robinson and Berridge (1993) the authors suggested to distinguish between the hedonic, i.e. pleasant, drug effects ("liking") and the feeling of craving for such a positive effect ("wanting"). Further, they attributed these effects to different neurotransmitter systems. They suggested that neurobiological effects associated with "liking" the drug are mediated by opioidergic neurotransmission in the ventral striatum, including the nucleus accumbens. This assumption was based on the observation that hedonic effects during consumption of a drug are caused by endorphin release in these brain areas – like during the consumption of primarily reinforcing stimuli such as food (Berridge & Robinson, 1998). Based on the work of Schultz and colleagues (1997), Berridge and Robinson further suggested that the neurobiological correlate of "wanting" is (phasic) dopamine release in the ventral striatum.
Following imaging studies intended to evaluate these aspects of the reward system - on a neurobiological as well as on a behavioural level by additionally using questionnaires for drug craving as a proxy for "wanting" beside scales measuring pleasure as a proxy for "liking". Indeed, studies suggested that acute drug craving is associated with dopamine dysfunction in the ventral striatum, i.e. reduced dopamine synthesis and D_2-receptor availability (Heinz et al., 2005b), while increased µ-opiate receptors in the ventral striatum correlated with other aspects of chronic alcohol intake and alcohol urges (Heinz et al., 2005a).

2.4 Memory formation

Striatal dopamine release is regulated by the hippocampus, which is well known to play a major role in memory formation (Lisman & 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). Experimental stimulation of the hippocampus may reflect real-life situations in which contextual, drug-associated cues activate the hippocampus and thus trigger memories associated with previous drug use (see Figure 3). In such situations, the activation of the

described hippocampus-VTA circuit will activate dopamine neurons in the VTA, which elicit dopamine release in the ventral striatum, thus facilitating new drug intake (Floresco et al., 2001). Indeed it has been shown that both cocaine and amphetamine sensitization (Goto & Grace, 2005; Lodge & Grace, 2008) increases hippocampal input in the nucleus accumbens, finally resulting in aggravated responses of the dopaminergic system.

Hyman (2005) argued that addiction somehow represents neuroadaptive processes in learning and memory that - under normal circumstances - serve to shape survival behaviour, i.e. behaviour related to the pursuit of rewards and the cues that predict them. Beside the possibility of synapse elimination and remodelling, the best known mechanisms of synaptic plasticity in learning and memory are such phenomena that change the strength or "weight" of existing connections, so called long-term potentiation and long-term depression. Although most of relevant research is based on animal models, long-term potentiation and depression have become important candidate mechanisms for the drug-induced alterations of neural circuits that are posited to occur with addiction in humans. There is evidence that both mechanisms occur in the nucleus accumbens and other targets of mesolimbic dopamine neurons as a consequence of drug administration, and growing literature suggests that they may play an important role in the development of addiction. The underlying molecular mechanisms include regulation of the phosphorylation state of key proteins, alterations in the availability of glutamate receptors at the synapse and regulation of gene expression (for review see e.g. Hyman & Malenka, 2001; Kauer et al., 2004; Thomas & Malenka, 2003).
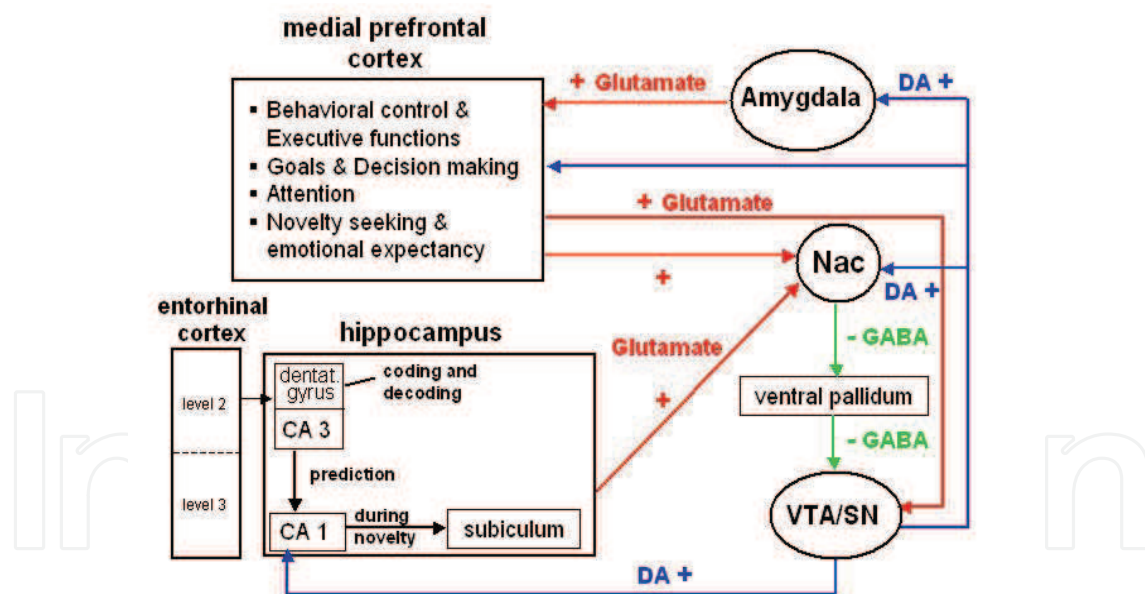

Fig. 3. A model of reward prediction in the brain: discrepancies between the expected and actual sensory input are recognized in the hippocampus. This activates dopaminergic neurons in the ventral tegmental area (VTA) via glutamatergic projections to the nucleus accumbens (Nac, incl. ventral striatum). The VTA in turn modulates neuronal transmission in CA1 region of the hippocampus via an increased dopamine-release and thus contributes to memory modification. The prefrontal cortex contributes to executive control functions and modulates the firing rate of dopaminergic neurons that project from the VTA region to the Nac and the amygdala (modified from Lisman & Grace, 2005).

3. Developing addiction

3.1 Criteria of addiction

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, 2000; World Health Organization, 2007). For the development of tolerance, it has been suggested that this phenomenon is based on a process of neuroadaptation in the brain to chronically increased alcohol or drug consumption. Continued drug intake leads to an anticipatory compensation of the drugs' effects by the brain, which results in a new homeostatic balance. This adapted state of equilibrium is disturbed when drug or alcohol intake is suddenly interrupted, as it is the case during detoxification. This can result in clinically manifest withdrawal symptoms, which are opposed to the drugs primary physiological and psychological effects (Koob, 2003). For instance, alcohols' sedative effects are mediated by inhibition of glutamatergic and stimulation of GABAergic neurotransmission (Tsai et al., 1995; Krystal et al., 2006). Insufficient GABAergic inhibition and increased glutamatergic excitation may result in highly aversive withdrawal symptoms and in epileptic seizures (Tsai et al., 1995; Krystal et al., 2006). Many imaging studies have focused on the neurobiological correlates of the defining characteristics of addiction in order to gain insight into the essence of the disease.

3.2 Craving

Within cue-reactivity paradigms, the reported correlations between subjectively reported craving and the actual consumptive behaviour are often low. This may in parts be explained by the different levels the reaction can emerge on (subjective, motor, physiological) and which are associated with different degrees of consciousness. Tiffany (1990) described a cognitive model in which conscious craving only occurs if an 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.

Unfortunately, imaging results regarding cue-induced activity in the brain and subjective craving for alcohol or other drugs are not very consistent. Myrick and colleagues (2004) reported an association between the severity of craving and functional brain activation in the ventral striatum, orbitofrontal cortex and anterior cingulate cortex, while others described such a relationship for the dorsal striatum (Modell & Mountz, 1995) or the subcallosal gyrus (Tapert et al., 2004). Further studies were not able to identify any significant correlation between alcohol craving and cue-induced brain activation (Grüsser et al., 2004; Heinz et al., 2004b). Trying to understand these diverging findings, one has to take into account that all studies used different stimuli for craving induction: alcohol-related words (Tapert et al., 2004), alcohol-related pictures with (Myrick et al., 2004) or without (Grüsser et al., 2004) a sip of alcohol ("priming dose"). Furthermore, time point of examination differed from patients being not detoxified (Myrick et al., 2004) to detoxified patients in an inpatient treatment program (Braus et al., 2001; Grüsser et al., 2004; Heinz et al., 2004b; Heinz et al., 2007; Wrase et al., 2002; Wrase et al., 2007).

3.3 Habit formation

For the development of addiction, specifically for reduced control of drug intake, it is of high relevance (Robbins & Everitt, 2002) to understand the behavioural transfer from

conscious consumption to a more automated behaviour, i.e. forming a habit (Tiffany, 1990). 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.

The importance of habitual drug intake for the development of addiction appears to be reflected in anatomical changes associated with cue-induced activation: whilst reward-driven striatal reactivity is known to predominantly involve the ventral striatum, cue-induced conscious craving in addicted subjects may preferentially elicit dopamine release in more dorsal striatal structures (Volkow et al., 2006; Wong et al., 2006). Such a transition from a predominantly ventral response to the dorsal striatum might reflect a change from a reward-driven activity of the ventral striatum to a more automated stimulus-response habit formation depending on dorsal striatal activity (Berke & Hyman, 2000). The rewarding effect of e.g. ventral striatal dopamine release may play a subordinate role in such automated processes, what is in line with the clinical impression and reports of patients. In accordance, Robbins and Everitt (2002) proposed that the initially reinforcing effect of drugs of abuse is based on the activation of the ventral striatum, while the transfer into habitual drug-seeking is associated with activation of more dorsal striatal regions. Studies with PET could also support that assumption, since among addicted subjects, drug cues preferentially lead to dopamine release in the dorsal striatum and putamen (Volkow et al., 2006; Wong et al., 2006). In line with the research, many patients also describe their relapse in terms of automated actions and do not remember to have experienced craving before relapse as in earlier stages of disease development (Tiffany, 1990).

3.4 Neurochemical adaptation underlying the development of addiction

Different neurotransmitter systems are involved in the processing of rewarding stimuli in general and of addiction-related phenomena in particular (see 1.3. for an overview). For a long time, neurobiological research on addiction mainly focussed on dopamine dysfunctions but in the recent past it has broaden its view on other neurotransmitter systems.

Brain imaging studies with PET clearly showed a reduced availability and sensitivity of central dopamine D_2-receptors in alcohol-dependent patients – potentially reflecting a compensatory down-regulation after chronic alcohol intake, which was associated with the subsequent relapse risk (Heinz et al., 1996; Volkow et al., 1996). Following PET studies (F-DOPA PET) revealed that alcohol craving was specifically correlated with a low dopamine synthesis capacity and with reduced dopamine D_2-receptor availability in the ventral striatum including the nucleus accumbens (Heinz et al., 2004b; Heinz et al., 2005b). Animal experiments also showed that extracellular dopamine concentrations decreased rapidly during detoxification (Rossetti et al., 1992). Thus, dopamine dysfunction may further be augmented by reduced intra-synaptic dopamine release during early abstinence. Another PET study (Martinez et al., 2005) showed that dopamine release in detoxified alcoholics was significantly reduced following amphetamine administration. Thus, overall dopaminergic neurotransmission in the ventral striatum of alcohol-dependent patients was reduced after detoxification. Unlike suggested by Robinson and Berridge (1993), it thus might seem unlikely that the appearance of a drug-associated cue can cause a significant dopamine release triggering craving or relapse. Indeed, animal studies demonstrated that alcohol and drug-associated stimuli can lead to relapse even if no dopamine is released in the ventral

striatum (Shalev et al., 2002). Nevertheless, a down-regulation rather than a sensitisation of the dopamine system appears to play a role in relapse behaviour: In humans, dopamine dysfunction was correlated with the severity of alcohol craving and with increased processing of alcohol-associated cues in the anterior cingulate and medial prefrontal cortex (Heinz et al., 2004b), brain areas in which an increased reaction on alcohol cues has been associated with an increased relapse risk (Grüsser et al., 2004).

Structural changes in striatal GABAergic neurons have also been considered to account for phenomena of long-term sensitisation towards the effects of drugs and drug-associated stimuli. Striatal GABAergic neurons are innervated by dopaminergic neurons and play a major role in the signal transfer towards the thalamus and the cortex (Robinson and Kolb, 1997). E.g., alcohol consumption stimulates GABA receptors and inhibits the function of glutamatergic NMDA-receptors (Kalivas & Volkow, 2005; Krystal et al., 2006). The alcohol-induced inhibition of the glutamatergic signal transduction results in up-regulation of NMDA receptors (Schumann et al., 2005; Tsai et al., 1995). As a consequence, the loss of this inhibition of NMDA receptor function via alcohol during early abstinence was related to hyperexcitation and withdrawal symptoms (Spanagel, 2003). Repeated withdrawal in turn elicits an increase in glutamate release (Kalivas et al., 2005). Therefore, it has been suggested that glutamatergic neurotransmission in a brain network spanning the prefrontal cortex, the amygdala, the hippocampus, the nucleus accumbens and the ventral tegmental area plays a major role in triggering relapse (Kalivas et al., 2005). Pharmacological treatment strategies pick up such findings, e.g. acamprosate, a drug used to reduce relapse risk in alcohol-dependent patients, diminishes alcohol craving via modulation of NMDA-receptors (Mann et al., 2004; Spanagel, 2003).

As already noted, the cannabinoid and opioidergic system also play a role in the development and maintenance of addictive behaviour. High concentration of CB1-receptors have been described in relevant brain regions, in detail in the prefrontal cortex, the amygdala, the ventral tegmental area, the hippocampus, the nucleus accumbens and the ventral striatum. In animal models of excessive nicotine and methamphetamine abuse, blockade of CB1-receptors reduced drug intake during relapse (De Vries & Schoffelmeer, 2005). Therefore, CB1-receptors are thought to modulate the activity of other neurotransmitters (dopamine, GABA and glutamate) and elicit long-term changes in synaptic transmission, in detail long-term potentiation or depression. Anyhow, further research is needed here to elicit the complex interplay of these neurotransmitter systems.

Within the opioidergic system, animal studies showed that blockade of μ-opiate receptors with naltrexone reduced dopamine release in the ventral striatum as well as alcohol consumption (Gonzales & Weiss, 1998). In humans, it has been shown that alcohol-dependent patients display an increase of μ-opiate receptors in the ventral striatum, which was further significantly correlated with the amount of craving (Heinz et al., 2005a). In line with that, application of the opiate antagonist naltrexone in humans can reduce alcohol craving and the subjective "liking" of the drug associated with its intake (O'Brien, 2005) and might reduce the risk of relapse in some patients (e.g. Srisurapanont & Jarusuraisin, 2005).

4. Risk of relapse

Detoxification itself does little to prevent subsequent relapse in alcoholics. Up to 85% of all patients relapse in the placebo control groups of treatment studies, even if treated as

inpatients until complete remission of physical withdrawal symptoms (Boothby & 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 that contributes to the risk of relapse is the exposure to stimuli that have regularly been associated with alcohol intake (contextual cues). Such stimuli have become conditioned cues that can elicit conditioned responses such as alcohol or drug craving and consumption behaviour (Adinoff, 2004; Berridge & Robinson, 1998; Di Chiara & Bassareo, 2007; Everitt & Robbins 2005). In such situations, patients may experience craving for alcohol or the specific drug, which is based on the natural tendency to avoid unpleasant experiences, e.g. a conditioned withdrawal response to the presentation of drug cues in the absence of drug intake. Indeed, about one third of all alcoholics in a clinical setting described that their relapse was preceded by a sudden manifestation of withdrawal. It often occurred long after acute detoxification and was often triggered by "typical" drinking situations (Heinz et al., 2003).

Although some imaging studies investigated the association between brain activation elicited by alcohol-associated stimuli and alcohol craving (see also 3.2), only few studies assessed to what extent cue-induced brain activation can predict the prospective relapse risk and therefore the clinical relevance of such imaging studies. Braus and colleagues (2001) reported that alcohol cues elicited increased activation of the ventral striatum and visual association cortices in detoxified alcoholics, and that patients who had experienced multiple relapses in the past showed a stronger cue-induced activity in the ventral striatum than patients who successfully abstained from alcohol for longer periods of time. This result was confirmed by Grüsser and colleagues (2004), who compared subsequently relapsing with abstaining patients. The latter group showed less brain activation elicited by visual alcohol-associated stimuli in the anterior cingulate cortex, the adjacent ventral and medial prefrontal cortex and central parts of the striatum. As the striatum, mainly the dorsal part, has been suggested to be crucial for habit learning, this result might reflect differences in the habitual character of addictive behaviour between abstaining and relapsing patients, even in the absence of conscious drug urges ("craving"). These observations are in the line with studies in animals, 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). Thus, when talking about relapse risk, it seems to be of importance to distinguish between the neuronal correlates of habitual drug intake (i.e. without conscious craving) and drug-intake following the subjective feeling of craving.

Unfortunately, the empirical basis for coherence between craving for the substance of abuse and risk of relapse is not fully satisfying. Although animal models strongly support the hypothesis that conditioned drug reactions are involved in the development and maintenance of addictive behaviour as well as relapse (Di Chiara, 2002; Robbins &Everitt, 2002; Robinson & Berridge, 1993), studies in humans are rather heterogeneous. While some studies did not find a positive correlation between subjective i.e. conscious craving and relapse (Drummond & Glautier, 1994; Grüsser et al., 2004; Junghanns et al., 2005; Kiefer et al., 2005; Litt et al., 2000; Rohsenow et al., 1994), others did show significant correlations (Bottlender & Soyka, 2004; Cooney et al., 1997; Heinz et al., 2005b; Ludwig & Wikler, 1974; Monti et al., 1990). In contrast, changes in physiological parameters, including neuronal activation measured with functional imaging, seem to be more closely connected to relapse (Abrams et al., 1988; Braus et al., 2001; Drummond & Glautier, 1994; Grüsser et al., 2004;

Rohsenow et al., 1994). Linking relapse risk with physiological responses may therefore be a more promising approach, and was used in several studies.

To measure the effects of reactions to non-alcoholic, affectively positive and negative stimuli on the relapse risk, Heinz and colleagues (2007) briefly presented affective pictures to alcoholics versus control subjects while conducting fMRI measurements. The affectively positive pictures elicited increased brain activation in alcoholics in ventral striatum, which was negatively correlated with the subsequent relapse risk and may represent a protective factor against relapse.

Dysfunctions of brain areas associated with executive control of behaviour (see also Figure 3) may also contribute to relapse risk. Indeed, in methamphetamine-dependent patients, the subsequent relapse risk 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). Similarly, Brewer and colleagues (2008) reported in cocaine dependent patients undergoing a stroop task an increased activation in regions relevant for cognitive control, including the anterior cingulate cortex, dorsolateral prefrontal cortex, as well as in the parietal lobule, insula and striatum. Longer duration of self-reported abstinence correlated with the strength of the activation of the ventromedial prefrontal cortex, left posterior cingulate cortex, and right striatum, percent drug-free urine screenings correlated with striatal activation, and treatment retention correlated with diminished activation of dorsolateral prefrontal cortex. Despite these promising examples, to date only few imaging studied followed the approach to predict relapse risk from the activity of brain areas associated with executive control of behaviour.

5. Clinical implications

Previous research in addiction suggests different therapeutic consequences. First of all, functional imaging studies help to understand the course of addiction development from its beginning up to its manifest state. Further, it can help to identify patients who are particularly at risk to relapse. As the described imaging techniques such as fMRI and PET are rather expensive, the transmission of these results on the application of less complicated techniques, which assess physiological responses to drug-associated cues, might be useful, e.g. the affect-modulated startle response (Heinz et al., 2003). Physiological markers that reflect an appetitive response towards drug cues - such as the startle response - are also important to identify unconscious aspects of craving behaviour, because many patients deny subjective craving when being exposed to a drug-associated cue but show strong appetitive reactions when assessed with the startle response (Heinz et al., 2003).

Patients suffering from strong cue-reactivity and a high risk of relapse may specifically profit from specific psychotherapeutic treatments such as cue exposure. Although, cue exposure has repeatedly been investigated in evaluative studies on the average, this treatment approach does not seem to result in significantly better outcome than standard therapy with cognitive-behavioural therapy and supportive interventions (Kavanagh et al., 2004; Löber et al., 2006). However, cue exposure may work best among patients with strong neuronal responses to alcohol cues, i.e. the identification of a subgroup of such patients may help to provide successful treatment strategies.

Brain imaging is also used to assess the effects of additive pharmacotherapy on cue-induced neuronal activation patterns during abstinence (e.g. Hermann et al., 2006). Myrick and

colleagues (2008) were able to show that cue-induced activation of limbic brain areas is reduced by naltrexone and by the combination of naltrexone and ondansetron in detoxified alcoholics. Since alterations in the response to affective cues have been suggested to predict relapse (Heinz et al., 2007) these results may help to identify new pharmacological and psychological treatment strategies, such as the modulation of the central stress response (e.g. George et al., 2008).

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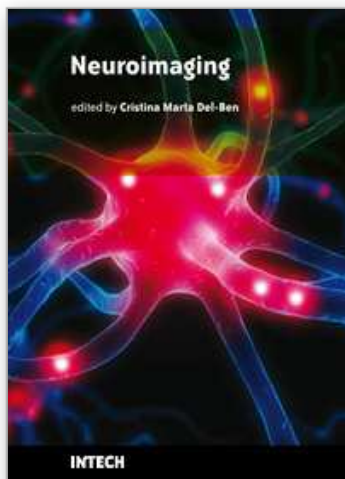
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Edited by Cristina Marta Del-Ben

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