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A THREE-PATHWAY PSYCHOBIOLOGICAL MODEL OF CRAVING FOR ALCOHOL

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Abstract — In this article, by reviewing the psychological, psychophysiological, neurobiological, and psychopharmacological literature on craving for alcohol, it is argued that converging evidence from several disciplines suggests a three-pathway psychobiological model of craving. Essential to this model is the appreciation of the role of individual differences in affect regulation strategies or personality styles, conditionability, sensitivity to alcohol's effects, and related dysregulations in distinct neural circuitries or neurotransmitter systems. These factors are of crucial importance to a proper understanding of the nature of craving, its underlying mechanisms and different manifestations. As a first pathway, it is suggested that *reward craving* or desire for the rewarding, stimulating and/or enhancing effects of alcohol might result from either dopaminergic/opioidergic dysregulation or a personality style characterized by reward seeking or a combination of both. As a second pathway, it is suggested that *relief craving* or desire for the reduction of tension or arousal might result from either γ-aminobutyric acid (GABA)ergic/glutamatergic dysregulation or a personality style characterized by stress reactivity or a combination of both. *Obsessive craving*, the result of the third pathway, can be defined as lack of control over intrusive thoughts about drinking resulting in impaired functioning. This type of craving might result either from a serotonin deficiency or a personality style characterized by low constraint or disinhibition or a combination of both. The putative implications of this three-pathway model for the assessment of alcohol craving, diagnosis and treatment of alcoholism, and future research on craving, are discussed.

INTRODUCTION

Craving is a prominent feature of alcoholism that can persist for months or years after an addict's last alcohol intake (Mathew *et al.*, 1979). The construct of craving has occupied an important position in many conceptualizations of addictive behaviour from the outset of scientific studies of addictions (Tiffany, 1995). The use of craving as a key explanatory concept in aetiologic models of alcoholism first peaked in the 1950s and 1960s. Due to the subsequent rise of behavioural approaches to the study of addiction, that eschewed the use of intrapsychic concepts, craving as a key explanatory concept fell out of favour for over a decade. Since the 1980s and possibly even more so since the 1990s, there has been a tremendous resurgence of interest in the role of craving in addiction research. By now, it is widely believed that the development of craving plays a crucial role in the transition from controlled drinking to alcohol dependence (Wise, 1988; Robinson and Berridge, 1993), the mechanisms underlying relapse (Ludwig *et al.*, 1974), and the treatment of alcoholism (Volpicelli *et al.*, 1992; Drummond *et al.*, 1995; Littleton, 1995). However, many problems in the field of craving research remain unresolved. For example, although craving has been implicated in relapse, many patients report craving that is not followed by relapse, and only a proportion of patients who have relapsed report retrospectively that they had craving prior to relapse (cf. Tiffany, 1990; van den Brink, 1997). Furthermore, clinical studies provide substantial evidence supporting the efficacy of so called anti-craving agents, such as acamprosate (e.g. Sass *et al.*, 1996; Whitworth *et al.*, 1996; Geerlings *et al.*, 1997) and naltrexone (Volpicelli *et al.*, 1992; O'Malley *et al.*, 1996*b*) in reducing relapse rates, yet the mechanisms underlying their efficacy are poorly understood (Spanagel and Zieglgänsberger, 1997) and the literature lacks hypotheses about the

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clinical features of those who are most likely to respond to either or both compounds and those who are not.

Obviously, the field of craving research is handicapped due to the concept's controversial conceptual status and the application of a wide range of scales and questionnaires of unknown reliability and/or validity (e.g. Tiffany, 1997). However, equally if not more importantly, the field is held from progression because craving studies have typically not taken into account individual differences with respect to the mechanism(s) underlying craving (cf. Niaura *et al.*, 1988). A growing body of evidence suggests that heterogeneity with respect to the psychological and neurobiological determinants of alcohol craving might have important differential treatment implications. In this article, by reviewing the psychological, psychophysiological, neurochemical, and psychopharmacological literature on craving, we will argue that converging evidence from several disciplines suggests a three-pathway psychobiological model of craving. Essential to this model is the appreciation of the role of individual differences in affect regulation strategies or personality styles, conditionability, sensitivity to alcohol's effects, and related dysregulations in distinct neural circuitries or neurotransmitter systems. These factors are of crucial importance to a proper understanding of the nature of craving, its underlying mechanisms and different manifestations. Below, we shall focus on data from the alcohol literature, but we draw selectively on the cocaine, opiate, and nicotine literature to illustrate points where alcohol data do not exist. Implications for assessment, treatment, and future research are also discussed.

PHENOMENOLOGY OF CRAVING

Examination of the literature on craving reveals that the entity has been conceptualized in a variety of ways, each with implications for suitable research techniques (Kozlowski and Wilkinson, 1987). For example, the construct has been used to subsume phenomena such as recurrent and persistent thoughts about alcohol, the struggle to control these drives, cognition and behaviour patterns similar to those in patients with obsessive–compulsive illness, urgent and irresistible desires, behavioural impulses, withdrawal symptoms, desire for alleviation of unpleasant withdrawal symptoms, intent to use alcohol, anticipation of positive outcome, anticipation of relief from negative affect, lack of control over use, cue-induced autonomic responses etc. As a result, a variety of relatively distinct tools have been developed to measure craving, including self-report scales or questionnaires, physiological measures, as well as neuroimaging techniques. Self-report methods include single-item Likert scales (e.g. Drobes *et al.*, 1994), single-item visual analogue scales (Tiffany and Hakenewerth, 1991), and multi-item multidimensional questionnaires (Tiffany and Drobes, 1991; Tiffany *et al.*, 1993; Anton *et al.*, 1996; Singleton *et al.*, 1996). Physiological measures include, among others, heart rate, skin conductance, skin temperature, salivary responding, and cardiac interbeat interval. Finally, neuro-imaging techniques include functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

Clearly, the current conceptual status of craving reflects the lack of a comprehensive aetiological model that explicitly distinguishes correlates and/or core components (e.g. desire for alleviation of unpleasant withdrawal symptoms; urgent and irresistible desires) from precipitants and/or causes of craving (e.g. withdrawal symptoms; cue-induced autonomic responses) on the one hand and consequences of craving on the other hand (e.g. lack of control over use; behavioural impulses). Conceptualization strategies based on overinclusion potentially add to the confusion in the field. For example, including potential consequential factors of craving in its definition creates the danger of tautological reasoning and thus of not being able to use the construct in an explanatory way, i.e. as a predictor of alcohol use or relapse (cf. Tiffany, 1990; Schippers *et al.*, 1997). Furthermore, including potential precipitating factors in the definition of craving creates the danger of ignoring clinical heterogeneity. For example, models proposing that craving can be indexed across three classes of behaviour, i.e. verbal report (or symbolic craving), overt behaviour, and somatovisceral response (or non-symbolic craving), and thus assuming that associations across these classes of responses are high, are generally not supported (cf. Tiffany, 1990). Based on the then available findings, Tiffany (1990) suggested that the processes that control drug-use behaviour operate independently of those responsible for urge responding. Equally plausible, however, is the possibility that a subgroup of substance abusers

experience craving associated with or resulting from (cue-induced) physiological arousal, whereas another subgroup experiences craving unrelated to physiological arousal (cf. Powell *et al.*, 1992). At least some of the inconsistencies and controversies with respect to the conceptualization and operationalization of craving might be resolved when potentially important individual differences are taken into account.

We are in agreement with Kozlowski and Wilkinson's (1987) arguing that the term craving should, consistent with its original meaning and its use in 'ordinary' language, be used only to refer to strong desires or urges to engage in some consummatory behaviour. Thus, craving for alcohol refers to strong desires or urges to drink alcohol. In addition, we would like to emphasize that the term should not be *a priori* restricted to a particular underlying or causal mechanism. Accumulating evidence suggests that craving can arise from a multitude of distinct factors, including neurochemical dysfunction, psychological needs, and psychophysiological symptoms. Many definitions tend to emphasize only one of these sources. For example, some investigators have defined craving as similar or identical to the symptoms of withdrawal (e.g. Marlatt, 1978) or as a correlate of a subclinical, conditioned withdrawal syndrome (e.g. Ludwig *et al.*, 1974). However, (conditioned) physical withdrawal phenomena reflect in fact only one possible mechanism that might underlie craving experiences (cf. Kozlowski and Wilkinson, 1987; Niaura *et al.*, 1988; Tiffany, 1990). Furthermore, it has often been argued that craving refers to an anticipatory, motivational state associated with a strong desire for a particular expected positive outcome, e.g. relief of negative affect or enhancement of positive affect. To carry this conceptualization to its extreme would be to redefine craving purely as a form of psychological attachment, based on the individual's cognitive capacities to anticipate, expect, and desire the effects of a given activity or substance that have yet to occur. There is, however, no evidence supporting the *a priori* emphasis on the anticipatory, expectant qualities of craving. Such a definition would not include the recurrent and persistent thoughts about alcohol — observed in many alcoholics — that reflect a type of craving that is less clearly motivated through the conscious anticipation of any particular outcome. Furthermore, by emphasizing the cognitive–motivational component of craving, we are moving the definition away from its potential physiological or somatic roots (cf. Marlatt, 1987). Craving may arise from an endogenous physiological need deriving from some biochemical deficiency or imbalance and an individual may experience craving without anticipating any particular outcome.

Another important *a priori* assumption about craving that potentially adds to the confusion is its presumed classically conditioned nature. Classical conditioning theory is considered a prominent explanatory model for craving (Franken *et al.*, 1998). Most likely, the frequent use of the cue exposure paradigm in craving studies has added to its prominence. Yet there is no evidence rejecting the possibility of craving as an unconditioned response. Individuals low on conditionability or without a reinforcement history sufficient enough to show classically conditioned responses, might well be motivated strongly to drink alcohol for any of its reinforcing properties. Such an explanation of craving would be consistent with an operant conditioning model of craving (Franken *et al.*, 1998).

In summary, a proper definition of craving for alcohol should be restricted to subjectively experienced strong desires or urges to drink alcohol and, for the sake of conceptual clarity and the construct's usefulness as a predictor of alcohol abuse or relapse, should exclude potential precipitating and consequential factors. *A priori* predictions about its nature, such as an emphasis on its supposed anticipatory/expectant qualities or conditioned status, have the potential to interfere with recognition of the potentially important role of individual differences with respect to aetiological pathways.

PATHOGENESIS OF CRAVING

Psychological findings

Recent psychological approaches towards understanding the role of craving in the initiation and maintenance of drinking behaviour include affective models focusing on affective states as the primary driving force for drinking (e.g. Baker *et al.*, 1987), motivational models focusing on drinking motives (e.g. Cox and Klinger, 1990; Cooper *et al.*, 1995), cognitive models focusing on the expected positive effects of alcohol (e.g. Stacy *et al.*, 1990; Wiers *et al.*, 1997), and the cognitive information processing model by Tiffany (1990).

Affective factors. Baker *et al.* (1987) proposed a dual affect model of cue reactivity, positing that reactivity to substance-relevant stimuli is controlled by complex affective processing systems that can be either appetitively based (positive affect craving systems) or withdrawal based (negative affect craving systems). Positive affect craving is assumed to result from an appetitive motivational system that can be activated by positive affect, cues previously paired with substance use, information that the drug is available, and a small dose of the substance itself. Once activated, this craving system produces craving report, positive affect, psychophysiological responses consistent with the stimulating effects of the substance, and substance-seeking behaviour. Similarly, negative affect craving is assumed to be strongly associated with withdrawal symptoms that can be activated by negative affect, cues associated with withdrawal, information that the drug is not available, aversive events, and physiological withdrawal signs. Once activated, this craving system produces craving report, negative affect, withdrawal symptoms, and substance-seeking. Importantly, it is proposed that the craving systems are structured within networks that encode information on eliciting stimuli, substance-related responses, and the meaning of stimuli and/or responses. These networks will be mobilized to the extent that the prevailing cue configurations provide a sufficient match for the encoded information: as the stimulus conditions approximate the prototype, the magnitude and coherence of activated responses will become greater. So, for example, induction of positive mood and presentation of relevant cues should produce stronger responses and stronger associations between various craving elements (e.g. autonomic arousal and self-reported craving), than would be elicited by either of these cues presented in isolation. Furthermore, it is hypothesized that the positive affect and negative affect craving systems are mutually inhibitory, such that stimulation of one network suppresses the activation of the other. Evidence supportive of the dual affect model of cue reactivity can be derived from studies showing: (1) the facilitative impact of priming doses of drugs on self-administration (Steward *et al.*, 1984); (2) the association of some relapses with positive mood and other appetitive stimuli (Tiffany, 1995); (3) the impact of mood induction on urge elicitation (Tiffany and Drobes, 1990; Rubonis *et al.*, 1994; Cooney *et al.*, 1997); (4) the power of self-reported craving elicited through negative mood imagery combined with alcoholic beverage exposure, to predict time to relapse after discharge (Cooney *et al.*, 1997); (5) the inhibitory relationships between craving associated with positive affect and craving associated with negative affect (Zinser *et al.*, 1992). However, other studies designed to evaluate the model's predictions have yielded results discrepant with this conceptualization of cue reactivity (for an overview, see Tiffany, 1995). Most importantly, the available evidence generally indicates that induction of positive mood has little impact on urge elicitation (Greeley and Ryan, 1995). Furthermore, factor analytic studies of multi-item craving questionnaires generally reveal that item sets reflective of anticipation of enhanced positive mood from drug use and those indicating anticipation of relief from negative mood and withdrawal are positively correlated, thereby challenging the hypothesis that positive affect and negative affect urges are mutually inhibitory (e.g. Tiffany and Drobes, 1991).

Motivational factors. Cox and Klinger (1988, 1990) proposed that drinking motives can be meaningfully characterized along two underlying dimensions reflecting the valence (positive or negative) and source (internal or external) of the outcomes an individual hopes to achieve by drinking. Thus, individuals may drink to obtain a positive outcome (positive reinforcement) or to avoid a negative one (negative reinforcement). Moreover, drinking may be responsive to internal rewards, such as the manipulation or management of one's own internal emotional state, or to external rewards, such as social acceptance or approval. Crossing these two dimensions yields four classes of motives: (a) internally generated, positive reinforcement motives (drinking to enhance positive mood or well-being); (b) externally generated, positive reinforcement motives (drinking to obtain positive social rewards); (c) internally generated, negative reinforcement motives (drinking to reduce or regulate negative emotions); (d) externally generated negative reinforcement motives (drinking to avoid social censure or rejection). Recent empirical data support both the conceptual and predictive validity of Cox and Klinger's model (Cooper, 1994; Cooper *et al.* 1995). Briefly, it was found that the four motives accounted for 14 to 20% of the variance in quantity and frequency of alcohol consumption in adolescents.

Enhancement motives (positive-internal) and coping motives (negative-internal) were both significant predictors of drinking problems, with coping motives being the stronger of the two predictors (Cooper, 1994). Furthermore, strong support was reported for a motivational model of alcohol use, postulating that: (a) enhancement and coping motives for drinking are proximal determinants of alcohol use and abuse through which the influence of expectancies, emotions, and other individual differences are mediated; (b) enhancement and coping motives represent phenomenologically distinct behaviours having both unique antecedents and consequences (Cooper *et al.*, 1995). In a recent study evaluating the relationship between drinking motives, heavy drinking, and drinking problems, it was found that motives operated both indirectly through heavy drinking and directly to account for drinking problems. Both positive and negative reinforcement motives retained unique predictive power (Carey and Correia, 1997).

To the extent that craving refers to a motivational-anticipatory state, motives for drinking are presumably important precipitants of craving. Moreover, the above summarized findings strongly suggest individually different pathways to craving, i.e. via enhancement motives for drinking as opposed to via coping motives for drinking. Support for the prominent role of motivational-anticipatory elements in (the mechanisms underlying) craving can be derived from studies examining the factor structure of multi-item craving questionnaires. For example, an examination of the Alcohol Craving Questionnaire (ACQ; Singleton *et al.*, 1996) and the Desires for Alcohol Questionnaire (DAQ) revealed that these questionnaires consist of three factors, i.e. labelled 'negative and positive reinforcement', 'strong desires and intentions to use alcohol', and 'mild desires or intentions to use alcohol' (Love *et al.*, 1998). The former two of these three factors appeared to be strongly intercorrelated ($r = 0.71$ and $r = 0.66$ for the ACQ and DAQ, respectively) and to be negatively correlated to the latter factor (Love *et al.*, 1998). Furthermore, Tiffany and Drobes (1991) found that two factors best described the item intercorrelations of the 32-item questionnaire on smoking urges, both of which consisted of items reflecting the desire and/or intention to smoke as well as the anticipation of reinforcement from smoking (positive and negative reinforcement, respectively). These findings suggest that craving for alcohol is closely associated with the anticipation of reinforcement from drinking.

Cognitive factors. According to expectancy-based models of learning, the presentation of stimuli previously associated with reinforcement is presumed to elicit reinforcer-specific expectancies (Marlatt, 1985). These expectancies are hypothesized to have both informational as well as motivational or incentive components. For example, presentation of drug-paired stimuli to an addict should generate an expectation or anticipation that use of the drug will produce specific effects, such as pleasure, stimulation, relaxation or relief, as well as a desire for these particular effects. In essence, this model associates craving with the motivational features of positive outcome expectancies (Tiffany, 1995). Note that positive outcome expectancies include expectancies pertaining to both the positive and negative reinforcing properties of alcohol, as opposed to negative outcome expectancies, which are presumably unrelated to either. Factor-analytic studies of alcohol expectancies have revealed several relatively independent belief clusters, including that alcohol: (a) transforms experiences in a positive way; (b) enhances social and physical pleasure; (c) enhances sexual performance and experience; (d) increases power and aggression; (e) increases social assertiveness; and (f) reduces tension (Brown *et al.*, 1980; Wiers *et al.*, 1997). There has been little research specifically evaluating this expectancy-mediated model of craving and cue reactivity. Several investigators have shown that expectancies of positive outcomes from alcohol consumption tend to be significantly correlated, concurrently and prospectively, with alcohol consumption (e.g. Stacy *et al.*, 1990) and alcohol use disorders (Nishith *et al.*, 1997). In an attempt to evaluate the expectancy model for craving more directly, Powell *et al.* (1992) explored relationships between positive outcome expectancies and reactivity to opiate cues in detoxified opiate addicts. They found that positive expectancies of opiate use were associated with cue-elicited opiate craving, particularly expectancies pertaining to the potential benefits in terms of excitement/glamorousness and emotional relief. Interestingly, Cooper *et al.* (1995) found that alcohol expectancies directly predicted drinking motives as well as moderated the impact of personality factors and emotional experience on the motivated use of alcohol. They also found that negative emotionality and coping resources were

significantly associated with coping motives for drinking among high-expectancy individuals, but were unrelated among their low-expectancy counterparts. These data further suggest an important role of expectancies in craving systems.

Tiffany (1990) presented a cognitive processing model of cue reactivity suggesting that, as a result of a long history of practice, drug use behaviour in the addict becomes automatized. That is, like other automatized skills, drug use becomes fast and efficient, stimulus bound, cognitively effortless, difficult to impede, and capable of being initiated and completed without intention. Tiffany's model explicitly rejects the assumption that craving represents the central motivational process responsible for substance abuse. Urges and cravings are conceptualized as constellations of verbal, somatovisceral, and behavioural responses supported by non-automatic cognitive processes that are required in situations in which automatic processes have not or cannot be invoked to produce appropriate responses, e.g. when the individual is attempting or forced to withstand the addictive behaviour pattern. Thus, according to this model, the mechanisms linking substance-related stimuli to substance use operate relatively independently of the processes that control craving. Utilizing a dual-task procedure for the assessment of cognitive effort, two studies have tested the model's prediction that craving represents the activation of effortful, non-automatic cognitive processes and thus interferes with cognitive tasks performed simultaneously. One study (Cepeda-Benito and Tiffany, 1996) reported findings consistent with the model (i.e. slower reaction time during craving elicitation than in the control condition), whereas another (Bradizza *et al.*, 1995) did not.

Summary of the role of psychological factors. In summary, findings from psychological studies of the initiation of alcohol use and the transition into excessive drinking suggest a distinction between at least two pathways. Within either pathway, drinking is controlled by a coherent network of affective, motivational, and cognitive processes. One pathway is demarcated by positive affect, enhancement motives for drinking, and enhancement expectancies, whereas the other pathway is demarcated by negative affect, coping motives for drinking, and tension reduction expectancies. It can be argued that, parallel to these pathways, two types of craving are to be distinguished: craving for alcohol's enhancing/stimulating or positive reinforcing properties vs craving for alcohol's relieving or negative reinforcing properties. Since most of the findings from psychological studies are derived from non-clinical samples, these models should not be applied to alcohol-dependent individuals and/or patient samples without caution. For example, the role of emotional and cognitive/attentional undercontrol in (craving for) alcohol use is insufficiently elucidated by these models. Finally, Tiffany's (1990) cognitive processing model suggests that craving as an explanatory construct might apply most clearly to situations in which automatized behaviour patterns are blocked. Thus, according to this model, craving is assumed to play a prominent role in relapse mechanisms, rather than in the day-to-day maintenance of pathological drinking behaviours. It should be noted, however, that at least in some individuals the continuous use of alcohol might be well conceived of as a consecutive series of relapses, suggesting a key explanatory role of craving in such drinking patterns.

Psychophysiological findings

Cue-elicited physiological arousal and subjective craving. Several experimental studies demonstrated physiological or autonomic arousal in response to alcohol-related cues among alcoholics (Niaura *et al.*, 1988). Psychophysiological reactivity appears across a variety of measures, including increased heart rate, skin conductance, and salivation (e.g. Kaplan *et al.*, 1985; Cooney *et al.*, 1997). Published correlations between cue-elicited physiological arousal and subjective craving are generally far from perfect (see Tiffany, 1990 for a short review). The average correlation coefficient ranged from $r = 0.38$ (if negative correlations were allowed) to $r = 0.52$ (if negative correlations were excluded). The apparent lack of concordance is troublesome for craving theories that claim conditioned physiological responses to be the only or most important substrate for craving, such as in withdrawal-based conceptualizations of craving (e.g. Ludwig *et al.*, 1974). Unlike withdrawal models, appetitively based theories envision a *modest* degree of coupling between these two response systems, as it is assumed that they both index the activation of the same motivational state (cf. Stewart *et al.*, 1984; Drobes and Tiffany, 1997). It is therefore concluded that, based on the available data, the appetitive model is better

supported than the withdrawal model, both in alcoholics and nicotine users (Niaura *et al.*, 1988; Drobes and Tiffany, 1997).

Several alternative explanations for the lack of a strong concordance between physiological arousal and subjective craving can be derived from the available data. For example, Monti *et al.* (1987) found subjective craving report to be significantly correlated with anxiety report ($r = 0.62$) and a measure for sensory state awareness ($r = 0.47$). Furthermore, among salivary reactors, craving non-reactors had significantly less awareness of salivation than did craving reactors, suggesting that the level of concordance is a function of sensory state awareness (Monti *et al.*, 1993). The level of concordance also appears to be a function of the severity of alcohol dependence. Kaplan *et al.* (1985) found that increased skin conductance level and subjective reports of craving correlated significantly among alcoholic ($r = 0.39$), but not among non-alcoholic, subjects ($r = 0.15$), and the correlation was found to be greatest ($r = 0.68$) among more severely dependent alcoholics as defined by self-reported withdrawal symptomatology (Kaplan *et al.*, 1983). Furthermore, in a cue exposure study among alcoholics, McCusker and Brown (1991) found the heart rate, salivation, and subjectively reported arousal, stress and anxiety together accounted for 46% of the variance of subjective craving, with subjectively reported anxiety making the most significant contribution (19%). Post-hoc analyses revealed that physiological responsivity (as indexed by heart rate, salivation, and arousal) accounted for 48% of the variance of subjectively reported anxiety, suggesting that the association between autonomic responsivity and craving was substantially mediated through cue-elicited anxiety.

Individual differences seem to play a major role in cue reactivity (cf. Rees and Heather, 1995). In a study examining the effects of exposure to alcohol and induced negative moods in abstinent alcoholic individuals, Cooney *et al.* (1997) found those who were most reactive in the negative-mood conditions (both in combination with water and alcohol exposure) were likely to be more anxious and depressed, and were more likely to have previously been drinking in situations associated with unpleasant emotions. Furthermore, Eysenck's (1967) theory of personality makes specific predictions regarding individual conditioning potential among certain personality types. Introverts are presumed to easily acquire conditioned responses due to a higher level of cortical excitation, thus enhancing formation of excitatory associative links. In contrast, the cortical inhibition of extroverts would result in reduced potential to develop excitatory conditioned responses. Neuroticism, attributable to elevated and labile limbic and autonomic activity, is thought to enhance conditioning potential in both introverts and extroverts (Eysenck, 1967). Consistent with Eysenck's conditionability hypothesis, McCusker and Brown (1991) found the level of cue-elicited reactivity to be significantly correlated with introversion and neuroticism. That is, introverts demonstrated greater salivary responses, and higher scores on arousal and anxiety than extroverts, and those scoring high on neuroticism demonstrated greater salivation than their low-scoring counterparts. Furthermore, neuroticism and introversion predicted more of the variance on physiological responsivity measures than either the severity of alcohol dependence or number of years' drinking.

Additional hypotheses regarding individual vulnerability in cue reactivity can be derived from Gray's (1975, 1987) modification of Eysenck's model, again based on principles of conditioning. Gray has proposed that introverts are more susceptible to aversive reinforcement (or punishment), whereas extroverts are more sensitive to appetitive reinforcement (or reward). From this perspective, it can be predicted that, if cue-elicited craving resulted from conditioning to both appetitive and aversive cues, reactivity would be equally associated with extroversion and introversion, producing no net effect. Gray also argued that neuroticism enhances conditioning in both introverts and extroverts, and that impulsivity is associated with susceptibility to appetitive conditioning. Two studies among detoxified opiate addicts yielded some findings consistent with Gray's predictions: Powell *et al.* (1990, 1992) observed that neuroticism and impulsivity, but not extroversion, correlated with cue-elicited craving.

Cue responsivity might be enhanced in individuals with a positive family history of alcoholism (cf. Rees and Heather, 1995). The evidence for enhanced learning and/or conditionability to alcohol's effects in such high-risk individuals is limited, but some recent studies provide indirect support by indicating that sons of male alcoholics with multigenerational family histories of alcoholism (MFH) manifest increased sensitivity to both the

negatively stress response dampening effects of alcohol and the positively reinforcing psychostimulant effect of alcohol (Levenson *et al.*, 1980, 1987; Sher and Levenson, 1983). For example, these individuals have been shown to demonstrate exaggerated sober autonomic stress responses, in that they demonstrate elevated heart rate, digital blood volume amplitude, and muscle tension reactivity to novelty, threat, and aversive stimulation (Conrod *et al.*, 1995, 1997*a*). Ethanol intoxication dampens the exaggerated sober autonomic stress responses in MFH men (Finn and Pihl, 1987; Finn *et al.*, 1990). Furthermore, in these individuals, ethanol also produces a pronounced increase in resting baseline heart rate during the rising blood-alcohol concentration (BAC) limb, a response that corresponds with elevated post-ethanol plasma β-endorphin levels (Conrod *et al.*, 1997*b*). This particular response to alcohol intoxication may provide an index of incentive reward, specifically marking activation in the dopaminergically mediated 'behavioural activation system' involved in producing the positive affective response to psychoactive substances (see Conrod *et al.*, 1997*a*). Because of the association between familial risk and sensitivity to alcohol's reinforcing effects, it can be hypothesized that familial risk is associated with enhanced cue associative learning and responding (cf. Rees and Heather, 1995).

Recent data have suggested that sensitivity to the reactivity-dampening effects of alcohol does not only occur among MFH men, but is equally strong among men with high anxiety sensitivity. It was shown that alcohol significantly dampened heart rate reactivity to aversive stimulation in both MFH and high anxiety-sensitive men, yet did not in low anxiety-sensitive men without a family history of alcoholism (Conrod *et al.*, 1998). Furthermore, alcohol significantly reduced skin conductance level (an index of anxiety/fear dampening) in high anxiety-sensitive men, whereas the effect in MFH men was less pronounced. On the other hand, MFH men demonstrated elevated alcohol-intoxicated resting heart rates (an index of psychostimulation). These results were interpreted as reflecting a sensitivity to general stimulus reactivity-dampening effects of alcohol in both high-risk groups, yet population-specific sensitivities to the fear-dampening and psychostimulant properties of alcohol in the high anxiety sensitivity and MFH groups, respectively.

Another interesting recent study reported sensitivity to alcohol reinforcement on the one hand, and behavioural undercontrol or disinhibition on the other, to be powerful independent predictors of drinking behaviour in drinking but non-alcoholic young men, suggesting that ethanol sensitivity accounts for the portion of the relationship between familial history of alcoholism that cannot be accounted for by disinhibited personality (Conrod *et al.*, 1997*a*). Cluster-analysing their data, Conrod *et al.* (1997*a*) identified three groups that differed in the extent to which alcohol affected their global mood. One group of individuals particularly susceptible to the reinforcing effects of alcohol, 75% of whom were MFH men, reported enhanced mood (e.g. more elated, more confident, and more clear-headed) after alcohol consumption. Another group, exclusively consisting of MFH men and differentially characterized by disinhibited personality traits, reported no changes in mood when drunk. Finally, a third group, only 23% of whom were MFH men, reported mood dampening when drunk. Problem drinkers were most frequently among the first two groups. This finding suggests that at least two vulnerability pathways (i.e. a reinforcement-mediated pathway and a disinhibition-mediated pathway) may be at play in the genetic predisposition to alcoholism. A primarily reinforcement-mediated pathway would be consistent with the finding by Hill (1992) of a third subtype of alcoholism that resembles Cloninger's type 2 alcoholism to some extent (e.g. early onset) but appeared not to be related to antisocial personality.

Summary of the role of psychophysiological factors. In summary, several studies indicate that concordance of alcohol cue-conditioned physiological and emotional arousal on the one hand and subjective craving report on the other is most prominently present among a subgroup of alcoholic individuals, i.e. those with severe alcohol dependence, high sensory state awareness, and high neuroticism scores. This subgroup might represent only one pathway to (craving for) alcohol consumption, being primarily mediated through negative reinforcement (no familial alcoholism; high anxiety sensitivity and/or sensitivity to alcohol's fear-dampening properties). Another pathway to subjective craving, possibly less concordant with physiological and emotional arousal measures, might be primarily mediated through positive reinforcement (familial alcoholism; sensitivity to

alcohol's psychostimulant properties). Finally, a third pathway to alcoholism might be primarily mediated through disinhibition (familial alcoholism; low conditionability). The potential role of craving in the latter pathway needs further attention. In any case, the findings listed above imply that individual differences are of paramount importance to elucidate the mechanisms underlying subjective craving report.

Neurochemical findings

Depending on the dose ingested, ethanol can exert positive reinforcing effects as well as anxiolytic, analgesic, and sedative effects. The different effects are mediated through interaction with distinct neurochemical mechanisms. The focus for the neurochemical systems underlying craving for alcohol and alcohol reinforcement has been the neuronal circuitries of the opioidergic/dopaminergic system, the γ-aminobutyric acid (GABA)–glutamatergic system, and the serotonergic system (cf. Lewis, 1996).

Opioidergic/dopaminergic system. Alcohol-induced release of dopamine (DA) in the nucleus accumbens is associated with the motor stimulant and positive reinforcing effects of ethanol (Di Chiara and Imperato, 1988). Apart from its active role in mediating the reinforcing effects of psychoactive substances, the mesocorticolimbic dopaminergic system in the nucleus accumbens seems to have an important role in incentive motivational learning (Beninger, 1983). Furthermore, it is generally assumed that the action of endogenous opioid systems plays an important role in the increased DA release in anticipation or actual receipt of alcohol (Di Chiara and Imperato, 1988; Gerrits, 1995). Thus the two systems are closely associated in the neurochemical modulation of the reinforcing and/or motivational properties of ethanol. Recently, it has been shown that there is a genetic association between reduced P300 amplitude and the DRD_2 DA receptor A_1 allele in children at high risk for alcoholism (Hill *et al.*, 1998).

A possible mechanism underlying the involvement of the endogenous opioid system in alcoholism and craving is described in the 'opioid deficiency hypothesis', which suggests that individuals with a family history of alcoholism have inherited a deficiency in the basal activity of this system (cf. Volpicelli *et al.*, 1990; Gianoulakis *et al.*, 1996). In addition to basal opioid deficiency, high-risk individuals might demonstrate hypersensitivity to the effects of ethanol. Consistent with both the deficiency and hypersensitivity hypotheses, it has been shown that both alcohol-preferring mice and human subjects with a family history of alcoholism show lower basal levels of plasma β-endorphin associated with higher β-endorphin response following ethanol ingestion (Gianoulakis, 1996; Gianoulakis *et al.*, 1996). Thus, differences in the basal activity and response of the endogenous opioid system to alcohol among high-risk individuals may be important in determining their risk for excessive alcohol consumption. Opioidergic deficiency is not necessarily genetically determined. According to the 'endorphin compensation hypothesis' (Volpicelli, 1987), alcohol drinking might also compensate for deficiencies in endorphinergic activity following the discontinuation of uncontrollable aversive events. This hypothesis is based upon the observation that uncontrollable aversive events lead to secretion of corticotropin-releasing hormone, which stimulates the release of β-endorphin from the pituitary gland and hypothalamus (e.g. Rossier *et al.*, 1977). Long-term exposure to uncontrollability might then produce tolerance to increased endorphinergic activity and (sudden) discontinuation may lead to a relative deficiency of opiate receptor stimulation (Volpicelli, 1987).

Administration of opioid antagonists, such as naltrexone, decreases relapse to heavy drinking, most likely through a reduction of craving and/or the reinforcing effects of alcohol (O'Malley *et al.*, 1992, 1996*a,b*; Volpicelli *et al.*, 1992, 1995, 1997; Davidson *et al.*, 1996). However, according to the opioid deficiency hypothesis, opioid antagonists, by binding to the opioid receptors and blocking the effects of the endogenous opioid peptides, are creating an opioid deficiency and should increase the craving for alcohol instead of decreasing it. This apparent paradox may be explained by the high doses of opioid antagonists used, which were sufficient to occupy all opioid binding sites. Thus, even though alcohol-related cues or a priming dose of alcohol would increase the release of opioid peptides, they could not interact with their specific opioid receptors to mediate reward mechanisms that eventually lead to a decreased craving for alcohol and decreased relapse to heavy drinking (cf. Volpicelli *et al.*, 1992; Gianoulakis *et al.*, 1996).

GABAergic/glutamatergic system. According to a negative reinforcement-based model, craving can be conceptualized either as a component of (un)-conditioned withdrawal or negative mood, or as the anticipation of relief from withdrawal or negative mood. The first possibility (i.e. craving as a component) assumes high concordance with conditioned physiological cue reactivity, whereas the second possibility (i.e. craving as a result) does not. Since concordance is generally modest (cf. Tiffany, 1990), the available data favour the latter possibility. Consistent with this view, it has been found that about half of the variance of subjective craving is accounted for by cue-elicited physiological and emotional responses (as indexed by heart rate, salivation, arousal, stress, anxiety) (McCusker and Brown, 1991), and that negative affect imagery increases (independently from alcohol exposure) subjective craving, but not physiological reactivity (Cooney *et al.*, 1997).

Thus, the neurochemical mechanisms underlying craving as a motivational response to cue-elicited physiological and emotional arousal might best be conceived of as the neurochemistry of the arousal itself. The neurochemical basis of alcohol withdrawal has been consistently characterized as an increase in neuronal excitability associated with reduced inhibition via the GABA–benzodiazepine receptor system, changes of voltage-gated Ca^{2+} channels, and increased excitation via the excitatory neurotransmitter glutamate or, more specifically, the *N*-methyl-D-aspartate (NMDA) receptors (Samson and Harris, 1992). The combined effect of the inferred increased excitatory neurotransmission and decreased inhibitory neurotransmission may lead to a substantial amplification of the overall excitatory neurotransmission, as can be indexed by the ratio glutamate/GABA (cf. Tsai *et al.*, 1998). Furthermore, because of symptom overlap between some anxiety disorders and alcohol withdrawal, investigators have suggested that increases in sympathetic nervous system activity due to dysregulation and overactivity in the locus coeruleus may be a common feature of both anxiety disorders and alcohol withdrawal (George *et al.*, 1990). There is evidence of a GABA- and a benzodiazepine-mediated inhibition of the locus coeruleus, which would be consistent with the effectiveness of benzodiazepines in treating these disorders (Grant *et al.*, 1990; Romach and Doumani, 1997).

Thus, the neuronal circuitry of the glutamate and GABA systems has been implicated in negative reinforcement-based cravings (Lovinger *et al.*, 1989; Tsai *et al.*, 1995; Lewis, 1996; Littleton *et al.*, 1996). Further evidence for this hypothesis can be derived from studies testing the clinical efficacy of acamprosate, the Ca^{2+}-salt of *N*-acetyl-homotaurinate, demonstrating that alcoholic patients receiving acamprosate maintain abstinence significantly longer than placebo-treated patients (e.g. Sass *et al.*, 1996; Whitworth *et al.*, 1996). The precise mechanism underlying acamprosate's clinical efficacy remains unclear (cf. Berton *et al.*, 1998), but the available evidence thus far strongly suggests that acamprosate interacts with NMDA receptor-mediated glutamatergic neurotransmission in various brain regions, reduces Ca^{2+} fluxes through voltage-operated channels and possibly possesses GABA-like properties (Durbin *et al.*, 1996; Spanagel and Zieglgänsberger, 1997; Wilde and Wagstaff, 1997). It has been suggested that acamprosate most likely interferes with the negative reinforcing effects of alcohol via a reduction of the neuronal hyperexcitability that occurs during the withdrawal and post-withdrawal periods, as well as via inhibition of conditioned withdrawal or physiological reactivity induced by stimuli that are repeatedly paired with the state of withdrawal, an action which might also reduce craving (Littleton, 1995; Spanagel and Zieglgänsberger, 1997).

The confusion about the mechanism underlying the clinical efficacy of acamprosate is plausibly related to heterogeneity among alcoholics with respect to the neurochemical systems involved. Clinical efficacy studies have typically not taken this potential heterogeneity into account. We are aware of only one published randomized trial examining the efficacy of acamprosate vs fluoxetine in familial and non-familial alcoholics (Gerra *et al.*, 1992). Interestingly, the results showed that, whereas familial alcoholics responded differentially to fluoxetine treatment, acamprosate was only effective among non-familial alcoholics. Assuming that non-familial alcoholics are more likely to drink alcohol (primarily) for its self-medicating properties, this study provides some evidence that acamprosate specifically and differentially modifies negative reinforcement-based craving. Possibly, patients who experience symptoms of withdrawal are vulnerable to withdrawal because of their enhanced excitatory neurotransmission at

baseline or, in other words, enhanced excitatory neurotransmission might be a trait marker which identifies a specific group at high risk for alcoholism (Tsai *et al.*, 1998).

Serotonergic system. The serotonergic system has been a prime candidate in the search for a biological basis for alcoholism. Evidence for serotonergic dysfunction in alcoholism has been derived from studies of cerebrospinal fluid (CSF) levels of the 5-hydroxytryptamine (5-HT) major metabolite 5-hydroxyindol-3-ylacetic acid (5-HIAA), studies of platelet levels of monoamine oxidase, studies of plasma ratios of the 5-HT precursor tryptophan over other amino acids competing with it for brain entry, and studies of responsivity to serotonergic challenging agents such as the partial 5-HT postsynaptic agonist, *meta*-chlorophenylpiperazine (*m*-CPP) (cf. Buydens-Branchey *et al.*, 1997*a*). Furthermore, a wide variety of 5-HT agonists (i.e. agents that produce effects like those produced by 5-HT itself) markedly reduce alcohol consumption in animals (Naranjo *et al.*, 1986). In humans, selective 5-HT reuptake inhibitors (SSRIs) have been consistently shown to decrease the short-term alcohol consumption of mildly to moderately dependent alcoholics, the effects reported being considerably less potent than those observed in animals (e.g. Gorelick and Paredes, 1992; Balldin *et al.*, 1994). There are basically four potential mechanisms underlying the potential efficacy of SSRIs in the reduction of drinking, all of which imply an important role of craving as a mediator. Indirectly, serotonergic agents may reduce craving and drinking: (1) by decreasing the need for relief of negative affect through their mood-regulating (antidepressant) properties; (2) through counteracting DA deficiency; (3) counteracting serotonin deficiency. More directly, serotonergic agents may (4) reduce the obsessional components of craving. Below, these four possibilities are discussed consecutively.

The first possibility (i.e. mediation through the antidepressant action) is controversial. Based upon the observation that fluoxetine is effective in reducing depressive symptoms among alcoholics (Kranzler *et al.*, 1995; Cornelius *et al.*, 1997) as well as alcohol consumption by alcoholic patients with co-morbid major depression (Cornelius *et al.*, 1997) but not of non-depressed alcoholics (Kranzler *et al.*, 1995), it is plausible to suggest that the effect of SSRIs on alcohol intake is secondary to (and thus mediated by) their mood-regulating (antidepressant) properties (e.g. Naranjo *et al.*, 1995; Cornelius *et al.*, 1997). However, based on the observation that changes in consumption of, and craving for, alcohol in response to SSRIs or *m*-CPP administration are generally unrelated to changes in the level of depression and anxiety, others considered mediation through an antidepressant effect highly unlikely (Gorelick and Paredes, 1992; Buydens-Branchey *et al.*, 1997*b*).

The second possibility (i.e. mediation through counteracting DA deficiency) is supported by several studies reporting a fluoxetine-sensitive increase of tissue DA levels, suggesting that serotonin release may indirectly result in increased DA secretion (e.g. Callaway *et al.*, 1991). Fluoxetine's ability to counteract DA deficiency (see also under Opioidergic/dopaminergic system) offers a further possible explanation of the observation that fluoxetine is differentially effective in familial alcoholic patients (cf. Gerra *et al.*, 1992).

The third possibility (i.e. mediation through counteracting serotonin deficiency) is supported by studies showing that ethanol appears to increase serotonergic levels during acute intoxication and then subsequently reduces serotonergic activity to subnormal levels with a biphasic action (cf. Goodwin, 1985). Chronic alcohol abuse may also increase serotonin function, and, given these acute and chronic serotonergic effects of alcohol, it is also conceivable that individuals with constitutionally low serotonergic function take alcohol as self-medication against mood dysregulation (Verkes, 1998). The differential response of patients with familial alcoholism to the serotonin uptake inhibition induced by fluoxetine supports the hypothesis of a serotonin deficit running in the families of alcoholics (Gerra *et al.*, 1992).

The fourth possibility (i.e. a *direct* reduction of craving) is supported by several studies showing decreases in craving after the administration of *m*-CPP and the SSRIs zimelidine, viqualine, citalopram, and fluoxetine (e.g. Gorelick and Paredes, 1992; Buydens-Branchey *et al.*, 1997*a*,*b*). It should be emphasized, however, that data with respect to the impact of SSRIs on craving are limited to short-term observations. The mechanism underlying a direct impact of serotonergic agents on craving is not an easy one to understand. Naranjo *et al.* (1987) have suggested that SSRIs decrease craving by facilitating central satiety

signals. Anton (1996) suggested that the link between serotonergic dysfunction and craving might be obsessional thinking; he compared the drive to use alcohol and the patient's attempts to resist that drive with phenomena experienced by patients with obsessive–compulsive disorder (OCD). As indicated by the important role of serotonergic dysfunction in OCD (Hollander *et al.*, 1992) and the specific efficacy of serotonergic agents in the treatment of OCD (Goodman *et al.*, 1990), 5-HT may play a major role in obsessional thinking about, or craving for, alcohol (Anton, 1996). In support of such a link, studies using fMRI and PET to detect brain regions involved in cue-induced cocaine craving (cf. Grant *et al.*, 1996; Maas *et al.*, 1998) and provoked symptoms of OCD (e.g. Breiter *et al.*, 1996) revealed overlapping brain activity in the isocortical (later frontal), paralimbic (anterior cingulate, temporal cortex), and limbic (amygdala) regions.

Summary of the role of neurochemical factors. In summary, converging evidence suggests important roles of the neural circuitries of the opioidergic/dopaminergic, GABAergic/glutamatergic, and serotonergic systems in craving processes, with each neural circuitry being related to a different type of craving. The opioidergic/dopaminergic system most likely plays a role in the positively reinforcing (rewarding) effects of alcohol and, possibly, (cue-induced) appetitive states or craving. A deficiency in the basal activity of this system (either genetically or environmentally determined) and/or hypersensitivity of this system to alcohol's effects seem to be important vulnerability markers for appetitive craving and alcoholism.

Furthermore, the GABAergic/glutamatergic system is likely to be involved in the neuronal hyperexcitability underlying the physiological and emotional arousal experienced by individuals during acute alcohol withdrawal and, possibly, conditioned withdrawal and/or other anxious states. Subjective craving is probably best considered an emotional-motivational consequence, rather than a component, of such states. Although the state of neuronal hyperexcitability can result from (chronic) alcoholism, it is conceivable that enhanced baseline excitatory neurotransmission is a vulnerability marker for such states and, thus, for this type of craving.

Finally, the role of the serotonergic system in craving report is suggested by studies showing craving to decrease following administration of SSRIs. Three potential mechanisms may account for an indirect impact of SSRIs on craving, i.e. through stabilizing mood, or through counteracting DA and/or serotonin deficiency. It is also possible that SSRIs more directly decrease craving through reducing obsessional thinking. Nevertheless, more work is needed to further elucidate the role of the serotonergic system in alcoholism, to identify subgroups of alcoholics responsive to SSRIs, and to examine the mechanism underlying the efficacy of SSRIs in treating alcoholics.

INTEGRATION OF FINDINGS: EMERGENCE OF A THREE-PATHWAY MODEL

Table 1 provides an overview of multi-factorial models of (craving for) alcohol use. Remarkably, many authors suggest *two factors* underlying the desire or craving for drinking and/or *two types* of alcoholics each with their own drinking motive and/or reinforcement history. In addition to the *two-factor motivational model* (Cooper *et al.*, 1995) and the *dual affect model* (Baker *et al.*, 1987) mentioned above, Cloninger (1987*a*) proposed two types of alcoholism, each with specific clinical correlates (e.g. personality profile, drinking pattern) and clinical course; Wise (1988) and Littleton *et al.* (1996) distinguished between two different aspects of craving, i.e. positive vs negative, and suggested that these distinct aspects were differentially related to distinct neurochemical systems; Wiers *et al.* (1994) suggested a dual-pathway model of psychological mechanisms of enhanced risk of addiction in children of alcoholics, distinguishing between primary alcoholism in which behavioural undercontrol, externalizing psychopathology, and alcohol expectancies of enhancement and power-aggression are important mediators (most likely to occur in sons of male alcoholics with multigenerational family histories of alcoholism) vs secondary alcoholism in which negative affectivity, internalizing psychopathology, and alcohol expectancies of tension reduction are important mediators (most likely to occur in children of secondary alcoholics); Niaura *et al.* (1988) proposed the *dynamic regulatory feedback model of cue reactivity* that either positive or negative affect, together with contextual stimuli, activate urges, physiological

Table 1. Overview of multi-factorial models of (craving for) alcohol use

	Relief craving	Reward craving	Obsessive craving
Psychological pathways			
Expectancy model (e.g. Wiers *et al.*, 1997)	Positive outcome expectancies		
Dual affect model of cue reactivity (Baker *et al.*, 1987)	Negative affect craving (withdrawal based)	Positive affect craving (appetitively based)	
Two-factor motivational model (Cooper *et al.*, 1995)	Coping motives for drinking	Enhancement motives for drinking	
Psychophysiological pathways			
Three-factor reinforcement model (Conrod *et al.*, 1997*a*,*b*)	Sensitivity to alcohol's fear-dampening effects	Sensitivity to alcohol's psychostimulant effects	Mediation through disinhibition
Neurobiological pathways			
Opioid deficiency hypothesis (e.g. Gianoulakis *et al.*, 1996)		Opioid deficiency	
Ethanol hypersensitivity (e.g. Gianoulakis, 1996)		Ethanol hypersensitivity	
Endorphin compensation hypothesis (Volpicelli, 1987)	Environmentally determined endorphin deficiency		
Glutamatergic dysregulation (Tsai *et al.*, 1995)	Neuronal hyperexcitability		
Three-box neurobehavioural model (Anton, 1996)	Stress reduction — GABA/noradrenaline	Reward sensation — endorphin	Obsessional thinking — serotonin
Serotonin deficiency (e.g. Goodwin, 1985)			Mood dysregulation
Miscellaneous models			
Neurobiological learning model (Cloninger, 1987*a*,*b*)	Type 1 alcoholism	Type 2 alcoholism	
Two-factor neurobiological model (Wise, 1988)	Negative reinforcement craving	Positive reinforcement craving	
Neurobiological model (Littleton *et al.*, 1996)	Negative aspects of craving	Positive aspects of craving	
Dual pathway model (Wiers *et al.*, 1994)	Pathway of secondary alcoholism	Pathway of primary alcoholism	
Dynamic regulatory feedback model of cue reactivity (Niaura *et al.*, 1988)	Negative affect cue reactivity	Positive affect cue reactivity	
Two-factor personality and motivational model (Cox, 1987)	Alcohol controlling negative affect	Alcohol controlling positive affect	

responses, and positive outcome expectancies (the content being largely dependent on the nature of the precipitating affect) and, thereby, trigger (relapse into) substance abuse; and, finally, Cox (1987) proposed a *two-factor personality and motivational model* of why people use and abuse alcohol, suggesting that individuals at risk for alcoholism will use alcohol initially to enhance their positive affect but, as drinking experiences continue, alcohol's control of negative affect might become progressively more salient than its control of positive affect.

As Table 1 shows, two-factor models neither account for a third potential pathway to craving as suggested, for example, by the three-factor reinforcement model proposed by Conrod *et al.* (1997*a*,*b*), nor explain craving mediated through serotonin deficiency (e.g. Goodwin, 1985; Anton, 1996). Based on this overview, it can be proposed tentatively that the available empirical findings are most adequately and comprehensively described by three, rather than two, pathways to craving. In Fig. 1, we propose an aetiological, psychobiological model of craving, incorporating the same three pathways, i.e. labelled reward craving, relief craving, and obsessive craving, respectively. Each pathway comprises both a neurobiological and a psychological component, but it does not necessarily follow from our model that these respective pairs of components are closely interrelated.

Personality traits are assumed to play a crucial role in all three pathways to craving. As we have shown before, personality is a key explanatory construct in many psychological conceptualizations of craving, and might account for individually different responses to substance-related cues and/or individually different manifestations of craving. The putative importance of personality is consistent with the high prevalence of personality disorders observed in alcoholics and drug addicts (Verheul *et al.*, 1995, 1997; Morgenstern *et al.*, 1997; Rounsaville *et al.*, 1998) as well as studies showing that: (1) childhood personality predicts alcohol abuse in adults (e.g. Cloninger *et al.*, 1988; Sher and Trull, 1994; Caspi *et al.*, 1997; Masse and Tremblay, 1997); (2) personality disorders predict the onset of alcohol use disorders among adults (e.g. Johnson *et al.*, 1996); (3) personality disorders predict (time to) relapse in treated alcoholics (e.g. Verheul *et al.*, 1998); (4) substance abusers with borderline personality disorder experience craving more often as a result of negative emotional states, tension, social rejection and negative physical states, than non-borderline substance abusers (Kruedelbach *et al.*, 1993).

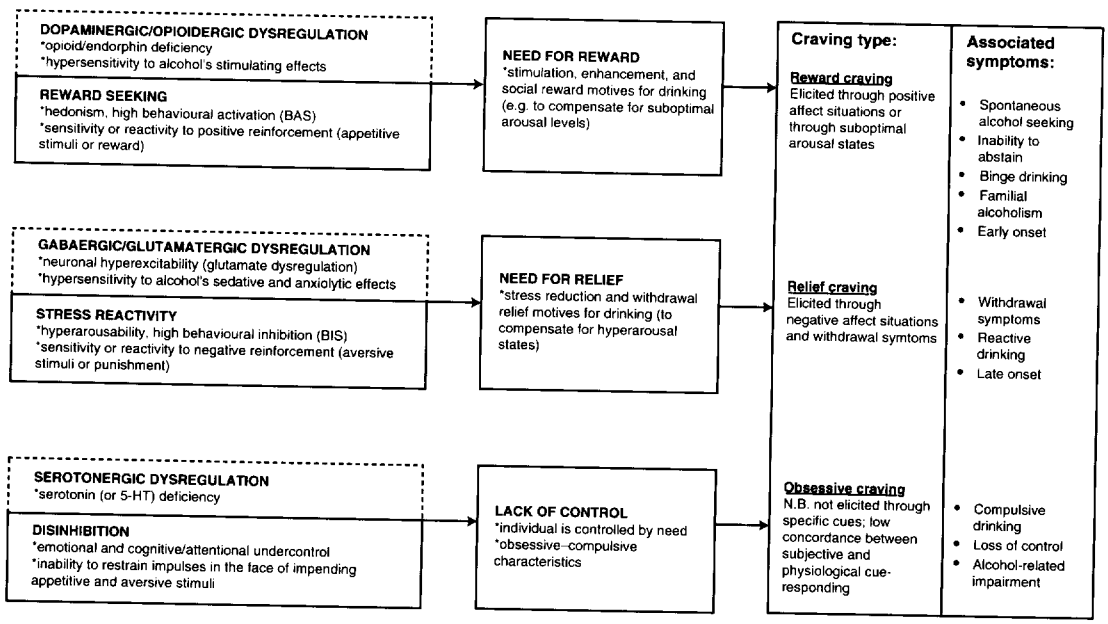

Fig. 1. Three-pathway psychobiological model of alcohol craving.

It should be emphasized that the model by no means aims to be definitive. Yet we think this model provides a heuristic framework that might stimulate further research by generating hypotheses. The respective pathways of the model will now be discussed.

Reward craving: pathway I

Reward craving or desire for the rewarding, stimulating and/or enhancing effects of alcohol might result from either dopaminergic/opioidergic dysregulation (neurobiological component) or a personality style characterized by reward seeking (psychological component) or a combination of both. From a neurobiological perspective, it can be hypothesized that either hypersensitivity to alcohol's stimulation effects (cf. Gianoulakis *et al.*, 1996) or suboptimal baseline levels of opioid and/or endorphin receptor functioning (cf. Volpicelli, 1987; Volpicelli *et al.*, 1990) predisposes to appetitive motives for drinking. From a psychological point of view, it is conceivable that this type of craving is associated with a personality style characterized by reward seeking and/or hedonism. This type of craving is also likely to be related to the psychophysiological system believed to control appetitive motivation, i.e. the appetitive or positive hedonic motivational system (Fowles, 1988). This system has also been called the behavioural activation system (BAS; Fowles, 1980; Gray, 1987). The major defined characteristic of this system is high sensitivity or reactivity to rewarding events or positive reinforcement.

In our view, the personality trait 'reward seeking' can be defined as the behavioural tendency to continuously seek positive reinforcement through stimulation and/or rewarding stimuli, such as substance use or social events, but that are not necessarily risky and/or thrilling. We would suggest reward seeking to be more strongly associated with the opioidergic/dopaminergic involvement in reward craving, than in 'positive emotionality', 'extraversion', 'novelty seeking' or 'sensation seeking'. Although positive emotionality has been found to be strongly associated with dopaminergic reactivity (Depue *et al.*, 1994), this personality trait (labelled interchangeably as either extraversion or positive affectivity; see Clark *et al.*, 1994) generally refers to a broad domain of personality traits (Digman, 1990), including personality facets (e.g. warmth, assertiveness, activity, and positive emotions) that might actually protect against addictive behaviours. Indeed, recent data showed that impulsive adolescents who were also characterized by low levels of positive affectivity used more alcohol and experienced more alcohol-related impairment than did impulsive adolescents with high positive affectivity or non-impulsive adolescents (Colder and Chassin, 1997). Furthermore, extroversion has been found to correlate negatively to craving (McCusker and Brown, 1991). In contrast, other facets of extroversion, such as gregariousness and excitement seeking, have been found among the characteristics that distinguish pre-alcoholics from other individuals (Cox, 1987). However, in our opinion, these two facets are not the essential personality correlates of reward craving. Excitement or sensation seeking, at the high end of the dimension, might actually be strongly correlated with the personality trait disinhibition or behavioural under-control that we explicitly distinguish from reward seeking. This would be consistent with the failure to find an association between the DA D_4 receptor gene and impulsiveness/monotony avoidance (Jönsson *et al.*, 1997). On the other hand, novelty seeking (Cloninger, 1987*b*), at least to the extent that it does not reflect the need to exhibit risky and/or dangerous behaviours, seems to conceptually overlap with reward seeking according to our definition. Studies linking the DA D_4 receptor gene with novelty seeking have yielded mixed results (Cloninger, 1998). In some studies (Ebstein *et al.*, 1996; Benjamin *et al.*, 1996), such a link was found, but in other studies these findings were not replicated (Malhotra *et al.*, 1996; Jönsson *et al.*, 1997; Sullivan *et al.*, 1998). Furthermore, one study found dopaminergic sensitivity (as indexed by growth hormone response) not to be associated with novelty seeking (Heinz *et al.*, 1996).

Reward cravers are sensitive to positive reinforcement. This does not necessarily imply that subjective craving and/or physiological cue reactivity can only become the conditioned response to positive affective situations. Since the individual might continuously seek rewards to compensate for a level of cortical arousal that is below one's optimal level, reward craving might as well become the (conditioned) response to suboptimal arousal states. It should be noted, however, that it will be considerably more difficult to distinguish between hypo-arousal-induced reward craving

and relief craving (see below), than to distinguish between positive mood-induced reward craving and relief craving.

Relief craving: pathway II

Relief craving or desire for the reduction of tension or arousal might result from either GABAergic/glutamatergic dysregulation (neurobiological component) or a personality style characterized by stress reactivity (psychological component) or a combination of both. From a neurobiological perspective, it can be hypothesized that neuronal hyperexcitability (as indexed by increased excitatory or glutamatergic neurotransmission, decreased inhibitory or GABAergic neurotransmission, or the combined effect of both) creates a basis upon which craving for relief from arousal is likely to grow. It is unknown to what extent the neuronal hyperexcitability can be attributed to an inherited tendency or, alternatively, to adaptive neuronal processes resulting from excessive alcohol use itself (cf. Tsai *et al.*, 1998). From a psychological point of view, it is conceivable that this type of craving is associated with a personality style characterized by stress reactivity, anxiety sensitivity, and/or hyperarousability. This type of craving is also likely to be associated with the psychophysiological system believed to control aversive motivation, i.e. the aversive motivational system (cf. Fowles, 1988). This system, inhibiting appetitively motivated behaviour in the presence of conditioned stimuli or cues signalling that aversive consequences will occur should the response be made, has also been called the behavioural inhibition system (BIS; Fowles, 1980; Gray, 1987). In an extensive review of animal studies, Gray (1977) argued that drugs with anxiolytic properties (including alcohol) reduce the reactivity or effectiveness of the aversive motivational system. Furthermore, evidence suggests that alcohol exerts an overall dampening effect on arousal, and it appears to modulate affective reactivity through its effects on higher order associative processes (Stritzke *et al.*, 1996).

In our view, the personality trait 'stress reactivity' can be defined as the anxious sensitivity to both external stressful events and internal physiological arousal. Presumably, stress reactivity is a construct close to 'anxiety sensitivity', defined by McNally (1990) as the fear of anxiety symptoms based on the beliefs that these symptoms might be dangerous or have harmful consequences, as well as 'trait anxiety', defined by the Five-Factor Model (FFM) of personality as the more general tendency to be apprehensive, fearful, nervous, tense, and jittery (Costa and McCrae, 1992). Possibly, stress reactivity is conceptually closely related to 'sensory-processing sensitivity', as described by Aron and Aron (1997). Sensory-processing sensitivity has been found to correlate strongly with alcohol sensitivity ($r = 0.39$; $P < 0.01$), as opposed to emotionality ($r = 0.18$; $P < 0.01$) (Aron and Aron, 1997).

It is conceivable to hypothesize that stress reactivity is the specific personality correlate of both relief craving and neuronal hyperexcitability (as indexed by the ratio GABA/glutamate), rather than 'neuroticism' or 'negative affectivity'. The latter concepts refer to a broad dimension of reactivity to negative stimuli (including impulsiveness and hostility), whereas stress reactivity is a more specific type of reactivity that overlaps with both, but is not entirely subsumed by them (cf. Clarke *et al.*, 1994).

Substantial evidence suggests that trait anxiety on the one hand and an inherited tendency towards decreased inhibitory (or GABAergic) and/or increased excitatory (or glutamatergic) neurotransmission on the other are closely related. For example, it has been shown that harm avoidance (Cloninger, 1987*b*) is strongly associated with plasma GABA ($r = 0.51$; $P < 0.001$; Cowley *et al.*, 1996). Furthermore, it has been shown that the function of the GABAergic system is impaired only in heroin addicts with co-morbid Axis II disorders from the anxious cluster and not in heroin addicts uncomplicated by Axis I or Axis II disorders, suggesting that there is a GABAergic deficiency independently of previous heroin consumption (Gerra *et al.*, 1998). Thus a subgroup of abstinent alcoholics might display low levels of plasma GABA. Three studies examining the association between familial alcoholism and GABA functioning suggest that it is unlikely that either low baseline plasma GABA or plasma GABA response to GABA agonists (e.g. diazepam) is associated with increased genetic risk for alcoholism (Moss *et al.*, 1990; Garbutt *et al.*, 1995; Cowley *et al.*, 1996).

Obsessive craving: pathway III

In our view, obsessive craving can be defined as lack of control over intrusive thoughts about drinking resulting in impaired functioning (as indexed

by amount of time occupied by alcohol-related thoughts, amount of resistance mounted against alcohol-related thoughts, and degree of control over alcohol-related thoughts) (cf. Modell *et al.*, 1992*a*). This type of craving might result either from a serotonin deficiency (neurobiological component) or a personality style characterized by low constraint or disinhibition (psychological component) or a combination of both.

It should be acknowledged that the serotonergic neurotransmitter system has been associated with many psychiatric illnesses and symptoms including impulsive aggression (e.g. Coccaro *et al.*, 1989), borderline personality disorder (Verkes *et al.*, 1996), suicidality (Coccaro *et al.*, 1989; Verkes *et al.*, 1997), OCD (e.g. Hollander *et al.*, 1992), and other anxiety disorders (cf. van Praag *et al.*, 1987). Serotonergic neurotransmission is complex: the level of 5-HT in the brain is only one mechanism by which behaviour may be affected; very different behavioural effects have been observed in relation to specific subtypes of 5-HT receptors (Murphy, 1990). However, although 5-HT disturbances might be non-specific from a nosological/categorical viewpoint, they might be rather specific from a functional/dimensional point of view. Across a multitude of psychiatric diagnoses, serotonergic dysfunction correlates with particular psychopathological dimensions, i.e. lack of control over regulation of behavioural impulses, mood and cognitive/attentional processes (cf. van Praag *et al.*, 1987). It can be argued that particularly emotional and cognitive/attentional under-control predispose to obsessive craving as described in our model, while behavioural under-control reflects a trait that sets any individual who experiences craving, regardless of type, at high risk for relapse.

As mentioned before, the serotonergic system may, more indirectly, be involved in other processes underlying craving, in particular through mood dysregulation. Due to its initial serotonin agonistic effect, alcohol might be consumed for its mood-stabilizing properties among those with a serotonin deficiency. Despite a distinct aetiological pathway, the craving resulting from such a mechanism would be phenomenologically similar to relief craving.

Consistent with the above, disinhibition (defined as the inability to restrain impulses in the face of impending appetitive and aversive stimuli) is possibly the most adequate description of the personality trait predisposing to obsessive craving. It should, however, be acknowledged that disinhibition has typically been studied in relation to impulse control disorders, rather than to obsessive thinking and/or OCD. Clearly, the observed association between craving and the serotonergic system needs further empirical elaboration.

Three pathways: discrete types or relatively independent factors?

Several attempts have been undertaken to distinguish between more or less discrete types of alcoholics. The most well known are Cloninger's (1987*a*) I/II typology and Babor *et al.*'s (1992) A/B typology. Whereas Babor *et al.* recognized the lack of total homogeneity within their subtypes inherent to the clustering procedure applied, Cloninger (1987*a*) did not explicitly admit the possibility of heterogeneity. However, attempts to replicate his typology in other populations of alcoholics have generally failed. For example, Koeter *et al.* (1995) reported that, by applying strictly the differential clinical features defined by Cloninger, only 7% of a sample of Dutch, residentially treated alcoholics fulfilled the criteria for either type I or type II. Presumably, the failure to dichotomously classify individuals according to two or more characteristics is related to the relative independence of the defining features. This is certainly true when the defining characteristics include personality traits, that are often distinguishable on the basis of factor analytically supported, relative independence. Another example is that of Cooper *et al.*'s (1995) attempt to classify their sample according to the two factors from their motivational model of alcohol use and abuse: only 25–30% of their sample could be successfully classified, whereas the majority of the subjects drank for neither or both reasons. In this case, the failure to classify subjects as either 'copers' or 'enhancers' was related to the correlation between the two scales for coping and enhancement drinking. From the above, we can learn that reality is better served by introducing relatively independent factors, that are allowed to simultaneously occur or be absent in individual cases. Distinguishing between relatively independent factors is also consistent with developmental models of addiction (e.g. Pandina *et al.*, 1984; Cox, 1987), which propose that the affective precipitants and consequences of alcohol abuse may change during the course of an individual's drinking career. Cox (1987) argued that many male pre-alcoholics

typically are not characterized by negative affective traits but, instead, by traits such as sensation and reward-seeking, need for immediate gratification, impulsivity, and unconventionality. Hence, they will use alcohol initially to enhance their positive affect, rather than to reduce their negative affect. However, as their drinking experiences continue, their chronic affect changes, the effect of alcohol on them changes, and their motivation for using alcohol changes. As a result, alcohol's control of negative affect becomes progressively more salient (Cox, 1987).

POTENTIAL CLINICAL IMPLICATIONS

Pharmacotherapy

Recent studies have shown acamprosate, naltrexone, and possibly SSRIs to decrease relapse rates and to prolong abstinence in weaned alcoholics, and it is suggested that these effects are due to the anti-craving properties of these compounds, while the mechanisms of action are supposedly distinct (see under Neurochemical factors). Our model predicts that naltrexone most likely reduces reward craving (possibly, through blocking the opioid receptors), whereas acamprosate might decrease relief craving (most likely, through a reduction of the neuronal hyperexcitability that accompanies withdrawal symptoms and/or anxious states). It is tentatively predicted that SSRIs might reduce obsessive craving. Furthermore, it can be predicted that those alcoholics who score high on reward seeking and/or hedonism and who are predominantly characterized by enhancement motives for drinking will respond differentially to naltrexone, those who score high on stress reactivity and/or anxiety sensitivity and who are predominantly characterized by coping motives for drinking will respond differentially to acamprosate, and those who score high on disinhibition and who are predominantly characterized by obsessive thinking about alcohol will respond differentially to SSRIs. These matching hypotheses have not yet been tested. Preliminary evidence indicates that the potential of acamprosate to prevent relapse does not apply to familial alcoholic patients (Gerra *et al.*, 1992) nor to antisocial (type 2) alcoholics (O. M. Lesch, personal communication), and that fluoxetine is differentially effective among familial alcoholics (Gerra *et al.*, 1992). These results suggest that distinct types of alcoholics show differential responses to acamprosate and fluoxetine. We are not aware of similar findings with respect to naltrexone.

Our model — being an attempt to dissect the syndrome (i.e. alcohol dependence) into its component parts — is a typical example of the functional orientation towards psychopathology advocated by, for example, van Praag (1990) and Soloff (1999). Given its functional/dimensional structure, our model has the potential to help direct treatment interventions, e.g. drug prescription, toward component psychological and/or neurobiological dysfunctions, rather than to the syndrome as a whole. As such, our model also supports the view that patients — when characterized by more than one dysfunction — might benefit from polypharmacological treatment. A recent study among heroin addicts showed that the combination of fluoxetine and naltrexone produces significantly greater retention than in patients given naltrexone alone (Landabaso *et al.*, 1998). This finding might be accounted for by additive effects upon distinct mechanisms underlying craving, which would support the above mentioned model. Alternatively, the observed effects might be explained in terms of pharmacokinetic interactions between the two compounds, possibly involving increases in plasma naltrexone concentrations via a fluoxetine-mediated effect.

Psychosocial treatment

A logical implication of a psychobiological model of craving in which reinforcement and conditioning processes are assumed to play an essential role, would be that therapeutic procedures based on extinction would decrease the probability of craving and, thereby, relapse. One potentially effective method to decrease craving and cue reactivity would be based on exposure with response prevention (Niaura *et al.*, 1988; Drummond *et al.*, 1995). In a recent randomized clinical trial, comparing the efficacy of cue exposure cognitive-behavioural therapy in moderating drinking, it was reported that cue exposure produced significantly greater reductions than cognitive-behaviour therapy in participants' reports of drinking frequency and consumption on each occasion (Sitharthan *et al.*, 1997). In another randomized clinical trial, it has been found that patients in cue exposure treatment had a more favourable outcome in terms of time to

relapse and total alcohol consumption than those in relaxation control treatment (Drummond and Glautier, 1994).

Accumulating evidence suggests that the intensity of urges elicited in experimental settings strongly depends on several characteristics of the cues used for exposure (Drummond *et al.*, 1995). For example, more intense craving and physiological reactivity have been reported in response to a combination of so called exteroceptive cues (e.g. a favourite drink) and interoceptive cues (e.g. a mood state) (Cooney *et al.*, 1997). According to our model, in which individual differences are considered the major determinants of the type and intensity of craving, it can be predicted that the efficacy of cue exposure treatment is associated with the extent to whether the treatment cues match those linked to drinking under individual life circumstances. To our knowledge, this hypothesis has not yet been tested.

IMPLICATIONS FOR ASSESSMENT AND DIAGNOSIS

A functional orientation towards the treatment of psychopathology requires a multifactorial (or multidimensional) approach to measurement and diagnosis. Potential candidates for multidimensional measurement of craving include the Alcohol Craving Questionnaire (ACQ; Singleton *et al.*, 1996) and the Desires for Alcohol Questionnaire (DAQ; see Love *et al.*, 1998). The items used in these questionnaires represent four (DAQ) or five (ACQ) areas relevant to alcohol craving, i.e. urges and desires to use alcohol, intent to drink alcohol, anticipation of positive outcome from drinking, anticipation of relief from withdrawal or negative outcome, and lack of control over use (ACQ only). It can be argued that the contents of these scales partly parallel the three craving pathways proposed in our model (see Table 1). Reward craving most plausibly correlates with the 'anticipation of positive outcome from drinking' subscale. Relief craving most plausibly correlates with the 'anticipation of relief from withdrawal or negative outcome' subscale. Obsessive craving might correlate with either 'urges and desires to use alcohol', 'intent to drink alcohol', or 'lack of control over use', or a combination of these subscales. It could also be argued that the Obsessive Compulsive Drinking Scale (OCDS; Anton *et al.*, 1996) and/or the obsessive subscale of the modified version of the Yale–Brown Obsessive Compulsive Scale (Y-BOCS-hd; Modell *et al.*, 1992*a*,*b*) are closely associated to the obsessive craving factor as posited in our model.

Examination of the factor structure of the ACQ and DAQ questionnaires revealed three factors, labelled as 'strong desires and intentions to use alcohol', 'no desire to drink', and 'negative and positive reinforcement' (Love *et al.*, 1998), suggesting a less clear fit with our model. In a study examining a similar craving questionnaire among nicotine addicts, a two-factor solution best described the items, i.e. one factor reflecting anticipation of pleasure from smoking as well as intention to smoke, and another factor reflecting anticipation of relief from negative affect and withdrawal as well as urgent and overwhelming desire to smoke (Tiffany and Drobes, 1991). The two factors appeared to have excellent internal consistency, but to be intercorrelated as well ($r = 0.71$). Apparently, the fundamental distinction between craving types, as proposed in our model, is not reflected by clearly separable factors in the questionnaires mentioned above. A tentative explanation would be that the instruments are not suitable to make the distinctions essential in our model, because the different pathways result in craving 'types' that are phenomenologically inseparable. Such an explanation would imply that the differentiation between the respective pathways towards craving cannot be made on the basis of measurement of the craving itself, but requires assessment of the underlying psychological, psychophysiological and/or neurochemical characteristics. For example, potentially relevant psychological characteristics include personality traits, motives for drinking, and alcohol expectancies, all of which can be reliably measured using self-report questionnaires. Psychophysiological and/or neurochemical measures might be obtained using provocation tests and/or drug challenges (see the research design below, for an example).

IMPLICATIONS FOR FUTURE RESEARCH

As mentioned before, our three-pathway model of craving provides a heuristic framework that by no means aims to be definitive, yet might stimulate

further research by generating hypotheses. The most obvious implication for future research is the potentially important role of individual differences to consider in any assessment of craving. From our work, it follows that individuals might be characterized by distinct pathways towards craving (aetiology) and, possibly, by distinct manifestations of craving (phenomenology). Presumably, these aetiological and phenomenological differences have differential treatment implications and should, therefore, not be ignored in any treatment efficacy study. The main problem at this moment is that we do not know for sure what pathways to, or manifestations of, craving should be distinguished. It might take decades of additional empirical effort to elucidate these issues more definitively. In the meantime, we recommend the assessment of potential clinical correlates (e.g. personality traits, motives for drinking, outcome expectancies, etc.) in any craving study. This will allow us to stratify statistical analyses in order to detect potential individual differences.

A further understanding of the psychological and neurochemical substrates of craving and cue-reactivity might benefit from several promising research designs, including both animal and human experimental studies. We will only highlight one that is currently planned by the authors. The primary objective of this study is to test a series of hypotheses on the neurobiology of reward vs relief craving, addressing the role of endogenous opioid systems in reward craving and the role of endogenous glutamatergic and GABAergic neurotransmission in relief craving. As a secondary objective, we will explore the clinical correlates (e.g. family history of alcoholism, personality traits, motives for drinking) of reward vs relief craving. The hypotheses will be tested indirectly in a human experimental study among 60 in-patient alcoholics who score high on scales for either reward *or* relief craving. This study will involve (positive and negative) mood induction and alcohol beverage exposure to measure cue-induced reward and relief craving, respectively, and placebo-controlled challenges with naltrexone and acamprosate to differentially modify the respective craving types. Furthermore, in a subsample ($n = 16$) fMRI will be used exploratively to locate brain regions that are involved in reward and relief craving. To examine the underlying neurochemical processes more directly, we will conduct a series of parallel animal experiments using a conditioned place preference model to measure positive and negative conditioned responses, placebo-controlled challenges with naltrexone and acamprosate to modify these respective responses differentially, and *in vivo* and *in vitro* autoradiographic procedures to measure activity of the endogenous opioid and glutamate/GABA systems related to reward and relief craving.

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