ALICE RAP WA3: WP8.2

Deliverable 8.2: Determinants of harmful substance use and harmful gambling: model and transition probabilities report

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Countries: The work was undertaken in the UK, Italy, the Netherlands, Denmark, Sweden, Spain and Germany, but is not country-specific.

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Participant organisations in ALICE RAP can be seen at http://www.alicerap.eu/about-alice-rap/partners.html

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1. INTRODUCTION

This is the second of three reports outlining the development of a series of models that map the determinants of different stages of addictive behaviour. These reports run in parallel to the evidence synthesis reports of the multidisciplinary group of Work Area 3 of ALICE-RAP. Work Area 3 (WA3) examines evidence surrounding the determinants of different stages of addiction, derived from expert reviews of the prevailing literature within a range of scientific disciplines. The disciplines that have contributed to this project are; anthropology, economics, genetics, neurobiology, public policy, psychology and sociology, with further input from experts on marketing, history, youth studies, cross-European perspectives and, finally, gambling.

WA3 examines three stages of the addiction process; 1) the transition from use or no use to risky substance use and gambling, 2) the transition from risky use to harmful substance use and gambling, and 3) reductions in harmful substance use and gambling. This report focuses on the development of models concerned with the second stage: transition from risky use to harmful use of substances and gambling. The aim of the model presented here is to demonstrate the available evidence concerning the determinants of harmful substance use and gambling in an easy-to-access format. The substances studies are alcohol, tobacco and illicit drugs and gambling is also included as a key example of behavioural addiction. The models are intended for use by policy makers and researchers within the addiction field, both to guide policy decisions and highlight areas for future research. By bringing together research in a visual format from the wide range of disciplines that inform addiction studies, we have been able to identify knowledge gaps where research is needed to improve our current understanding and facilitate the development of new multidisciplinary theories on substance use and gambling.

1.1 Model and Transition Probabilities- Aims and Approach

1.1.1 Model

The work presented her draws on a companion evidence synthesis report (Gell et al. 2012). This drew on evidence reviews from a range of scientific disciplines which study addiction to identify discrete determinants which influence an individual's progression from risky use to harmful use of substances or gambling. The aim of the present work was to provide a visual representation of these determinants and, furthermore, we wished to explore how evidence from multiple disciplines, which differ in their scientific approach, may be brought together into an accessible visual format. The key criteria applied when developing our model to enhance utility to both policy makers and researchers, were:

- Clear display of the range of determinants identified across all participating disciplines;
- Visualisation of determinants at different levels of abstraction;
- Demonstration of the relationships and dynamics between the different determinants;
- Identification of determinants that are researched by several disciplines and may be candidates for further research by multidisciplinary collaborations.

Through the models presented here, we are able to highlight evidence gaps and potentially important interactions between determinants identified in distinct disciplines which may be examined further in future multidisciplinary research. These models are intended for use by addiction researchers to aid in the process of hypothesis and theory development around risky use of addictive behaviours. We also envisage policy makers engaging with these models to improve the design and targeting of policy responses.

This report is structured as follows: First, we present and explain our working definition of harmful substance use and gambling and briefly explore how this is operationalised in our research. Subsequently, we describe the method for producing the models, including our definition of a determinant and how we extracted determinants of harm from each of the disciplines, the key themes within our model and the process of evidencing and validating the model. We do not describe the process of developing the generic model design, such as decisions around how to most effectively present data in the model and the level of abstraction of determinants, as this is described elsewhere (McLeod et al. 2013). Next, we present the model and describe key findings around determinants that vary by substance and those common to multiple disciplines. Finally, we discuss the limitations of our approach and implications for research and policy.

1.1.2 Transition probabilities

The literature based approach used in the synthesis report allows the investigation of as many factors as desired. The problem with literature reviews has been that while listing factors, which are potentially important, the interaction of different factors is not clear as different factors are listed in different papers and the relative importance of the different factors thereby requires a subjective judgment. Moreover, even if systematic reviews are done and data are quantitatively summarized in meta-analyses (e.g. Stroup et al. 2000), the numerical values given for different epidemiologic indicators are often inconsistent; incidence derived from a meta-analysis may be inconsistent with prevalence derived from another meta-analysis or with the known case fatality or duration rates. This had led to various efforts to model epidemiological parameters consistently, most formalized in the development of software to estimate key parameters of incidence, prevalence, duration, remission, and case-fatality in light of general population developments (http://winthrop.ihme.washington.edu/; see also Barendregt et al. 2003; Mathers et al. 2002). Such modern

modelling approaches are not possible for many factors as all the interactions between factors have to be integrated. Consistency requires limitation of factors, and concentration on the most important factors.

This report presents one of the first attempts to model transition probabilities for different stages of substance use. In D7.2 we presented transition probabilities for one of the most commonly used substances, alcohol. The current report presents different stages of nicotine use as another commonly used substance. As described above the modelling approach requires focus on a selective set of factors. Across multiple studies there are a few basic characteristics that have been shown to influence substance use in different stages of use, for example age and gender have consistently been shown to be related to almost all stages of alcohol consumption. But age (Hibell et al., 2012), gender (World Health Organization, 2011), and comorbidity (U.S. Department of Health and Human Services, 2004) also influence smoking behaviour and nicotine dependence, thus we use the same set of factors for calculating nicotine transitions as we used for alcohol. This will permit comparison between the results.

The aim of the transition probabilities in this report is to model the course of smoking behaviour. To describe the course of smoking over time, we have estimated transition probabilities from one stage to another. To start the model simple and test the feasibility of the modelling, we included only four factors: 1) stage of use (three categories: abstinence, use, harmful use) as an outcome variable, which of course in a final general population model would have to be supplemented by death, especially given the high relative risk of harmful use compared with the general population (Roerecke & Rehm, 2013), and three influencing factors: 2) age, 3) sex, and 4) co-morbidity. Conceptually, even though simple, this model is more complicated than the one currently most often used in epidemiological modelling, where only sex and age is controlled, and only two categories of outcome are involved: abstinence and use disorders (Whiteford et al. 2013). Given this framework, we try to estimate transition probabilities between the different categories of outcome which will allow us to track the course of a population over time.

1.2 Definition of harmful substance use and harmful gambling

Harmful substance use and gambling describes a behavioural state where an individual has progressed beyond the risky pattern of use (that was the focus of WP7) to actual experience or causing of harm. Harmful substance use and gambling was defined as:

"Substance use or gambling which has caused material harms of social, mental or physical nature which are experienced by the user, other individuals or society at large, where cause means outcomes which would not have occurred without the substance use or gambling".

The distinction between risky and harmful use can be conceptualised as the difference between behaviour that has the potential to cause harm and behaviour that is actually causing social, mental or physical harm. For example, an example of *risky* use in relation to alcohol consumption might be drinking to the point of intoxication, which can place you and those around you at risk of harms such as accidents and violence. *Harmful* use would be drinking to the point of intoxication and, as a result, actually experiencing harms such as being involved in a traffic accident or a violent fight. Thus harmful substance use or harmful gambling presupposes (a) that a negative consequence of behaviour is caused or experienced and (b) that the behaviour is a necessary cause of the outcome.

1.3 Overview of harmful substance use and harmful gambling

Our understanding of the nature of harmful substance use and harmful gambling is informed by our position as European societies which place a high value on economic productivity and on preserving individual physical health. Framed within this context, harmful substance use and gambling are problematic because they result in negative physical or mental health outcomes and economic, legal, financial or social costs for the individual, their family and friends or for wider society.

Before engaging in a description of harmful substance use and harmful gambling, it is important to acknowledge that there are benefits associated with substance use and gambling. For example, moderate alcohol consumption is associated in observational studies with health benefits including reduced risk of coronary heart disease (Corrao et al. 1999) and psychosocial benefits including sociability, mood enhancement and stress reduction (Peele & Brodsky 2000). However, substance use and gambling behaviour may be considered harmful where the total costs to the individual or society outweigh such benefits.

1.3.1 Harms to the individual common to addictive substances and gambling

As a result of consuming licit or illicit substances, or gambling, individuals may experience a range of negative health or non-health consequences. Potential non-health consequences of substance use and gambling include financial problems (such as debt or bankruptcy), domestic problems or the disruption of personal relationships (such as family disintegration and relationship breakdown), difficulties in obtaining and maintaining employment, and engagement in violent or drug-related crime (Advisory Council on the

Misuse of Drugs 2006; Shaw et al. 2007);(Reith 2006). Substance use and problem gambling may also impair psychological functioning and reduce quality of life (Costenbader et al. 2007; Grant & Kim 2005). Among individuals who use substances and gamble problematically, the prevalence of depression and rates of suicide are high compared with the general population (Reith 2006; Stenbacka et al. 2010).

Whilst many health consequences of substance use are specific to the drug in question, there are a number of health problems that are common to different modes of drug consumption. For example, consuming drugs via intravenous injection is associated with secondary harms (such as transmission of blood-borne viruses (such as HIV and Hepatitis B and C), septicaemia, abscesses, vein collapse and thrombosis) resulting from this mode of drug administration (Nutt et al. 2007).

1.3.2 Harms to the individual from different addictive substances and gambling

Harms to the individual specific to different addictive substances and gambling are predominantly health related harms: non-health consequences are often common to multiple licit or illicit substances and gambling (Advisory Council on the Misuse of Drugs 2006; Room 2005).

Many substances encourage repeated use, driven by various factors including the nature of the drug experience, their power to induce dependence and withdrawal reactions (e.g. Sayette et al. 2000). Some drugs, for example cannabis, result in a psychological dependence where habitual use is based on cravings rather than the drug withdrawal that is associated with the kind of physical dependence experienced by, for example, heroin users attempting to stop using. The half-life of a drug (the speed at which it is cleared from the body), the pharmacodynamic efficiency of the drug, and the degree of tolerance that develops from repeated use are all factors in the development of dependence and withdrawal. The strength of evidence on the tendency of different substances to induce dependency is varied as we have more population-based estimates of addictiveness for the more commonly used drugs. Research to date suggests that smoked tobacco is the most addictive commonly used drug, with heroin and alcohol somewhat less so. In contrast, psychedelics have a low addictive propensity (Nutt et al. 2007).

Evidence for harmful health consequences of substance use in relation to licit substances is well documented within epidemiological studies. Harmful alcohol users may experience a range of negative health outcomes including maternal and peri-natal disorders, cancer, neuropsychiatric disorders, cardiovascular diseases, cirrhosis of the liver, and unintentional or intentional injuries (Rehm et al. 2010). In 2004, it is estimated that 94,452 men and 25,284 women aged 15-64 years died of alcohol attributable causes in the EU,

corresponding to 11.9% of all deaths in that age range (Rehm et al. 2012). Deaths associated with alcohol dependence make up 71% of the net burden of alcohol-attributable mortality.

The negative health consequences of tobacco use are wide ranging and include cancers (such as oropharyngeal and laryngeal cancer), cardiovascular diseases (such as ischemic heart disease and heart failure) and respiratory diseases (such as pneumonia, influenza and chronic obstructive pulmonary disease)(Rehm et al. 2006c). In 2000, 18.0% of deaths (13,491,000 people) in developed regions of the world and 12.2% of the global burden of disease among men and women combined was attributable to smoking and oral tobacco use (Rehm et al. 2006c). For Europe, tobacco use contributes to the deaths of some 650,000 European Union (EU) citizens a year (World Health Organisation 2012).

Harms from illicit substance use are inextricably linked to the type of drug, the way it is used (e.g. intravenous versus smoked), the social context of use and how it is combined with other substances (Centre for Public Health 2011). Illicit substances, including cannabis, cocaine, opioids, nitrites and dissociative anaesthetics, are associated with a range of acute and chronic physical and psychiatric harms and we examine these in turn below.

Cannabis is a psychoactive preparation of the marijuana plant. Harmful cannabis use is that which results in physical morbidity such as irritant effects on the respiratory system, difficulty in motor-coordination and inhibition of reproductive functions, and psychiatric consequences such as impairment of higher cognitive functions and personality changes (Ashton 2001). No cases of fatal overdose from acute cannabis use have been reported but cannabis use has been implicated in driving fatalities and fatal cardiac accidents in young users. Cannabis use may be an important risk factor for chronic respiratory diseases such as chronic bronchitis and there are a number of reports in the literature of an association between cannabis use and rare forms of oropharyngeal cancer in relatively young users (Ashton 2001).

Opioids are psychoactive chemicals that have analgesic effects but can also create strong sense of euphoria. Harmful opioid use is associated with health problems that include urinary retention, depressed nervous system activity, sedation, mental confusion and hallucinations (Centre for Public Health 2011). Intravenous opioid use carries the greatest risk of addiction and health complications. Intravenous use is associated with additional risks such as the transmission of infectious diseases including HIV/AIDS, hepatitis B and hepatitis C, as described above (Rehm et al. 2006c). Mortality from opioid use may be a result of overdose or be linked to a range of complications including respiratory depression and profound decreases in blood pressure leading to respiratory arrest (Centre for Public Health 2011). Opioids, mainly heroin or its

metabolites, are present in the majority of drug-induced deaths reported in Europe, even if a substantial proportion of all drug-induced fatalities occur in a context of polydrug use (EMCDDA 2012). In 23 European countries providing data in 2009/10, opioids accounted for the overwhelming majority of cases, with 15 countries reporting proportions of 80% or more. Drawing on an analysis of data from over 30 cohort studies following patients up to 2010, it was estimated that 10,000–20,000 opioid users die each year in Europe, with most deaths occurring among males in their mid-thirties (EMCDDA 2012).

Stimulants are psychoactive substances such as amphetamines and cocaine that induce temporary enhancements in either mental or physical function. Some of the risks of stimulant abuse are illustrated here by focusing on the harms of cocaine. Both acute and chronic cocaine use are associated with a number of negative physical and psychological outcomes. Potential physical health harms of acute use include cardiovascular, respiratory, neurological and genitourinary complications and adverse psychological effects include personality or mood changes such as anxiety, sleep disturbance and paranoia (Kaye & Darke 2004). Acute complications may lead to death, for example as a result of toxic reactions which may lead to cardiac or respiratory arrest (Kaye & Darke 2004). Mortality from chronic cocaine use is most often linked to cardiovascular complications such as inflammation and injury of the heart muscle. Morbidity related to chronic cocaine use may affect a range of body systems including the vascular, renal, neurological and reproductive systems (Centre for Public Health 2011).

In addition to the harms of illicit substance use evidence supports an association between problem gambling and a number of chronic health problems. Although a direct causal relationship is not always evident, problem gambling is also associated with chronic medical conditions, obesity, and the use of expensive forms of medical care (such as psychiatric hospitalization)(Black et al. 2013).

1.3.3 Harms to others from addictive substances and gambling

The use of addictive substance and gambling may bring about harm or costs to those not engaged in the behaviour, such as the users' family or friends, as well as wider society.

The friends, family and wider social networks of harmful substance users or gamblers may experience a range of negative health and non-health consequences of the addictive behaviour. During pregnancy and early childhood there is a risk of harms to the foetus and the breastfeeding baby as a result of substance use, as well as risk of childhood neglect and abuse (Nutt et al. 2007). Intravenous drug use is associated with the transmission of blood-borne viruses and may harm others through the transmission of infection to sexual partners and needle-sharers (Nutt et al. 2007). Smoking, including nicotine and cannabis, is associated with

harms of passive or second-hand smoke (such as cancer and cardiovascular disease) (Advisory Council on the Misuse of Drugs 2006). Substance users may inflict verbal and or physical abuse on family and friends (Laslett et al. 2011). Research exploring the impact of drug use on family found that many reported declining physical and psychological health due to stress (Velleman et al. 1993) and had sought professional help for themselves to cope with stress (Melberg et al. 2011).

Wider society (and individuals within it) might also experience harm from others' substance use or gambling, for example through being a victim of crime. Alcohol intoxication is a common cause of car and other accidents (Nutt et al. 2007) and a contributory factor in violent crimes including homicide, sexual assault, robbery and assault.

Non-health consequences of association with a harmful substance user or gambler include reduced well-being from having to live with and suffer exposure to an intoxicated person (Nutt et al. 2007), fear of violence (Melberg et al. 2011) and being threatened or verbally abused (Laslett et al. 2011). Families of drug users have also described negative consequences such as the introduction of the family to crime and criminal activity (Nutt et al. 2007), exposure to drugs, altered family functioning (e.g. loss of close relationships) and theft of goods and money from the home (Barnard 2005). Outside of the user's immediate family and friends, negative consequences of alcohol use that have been reported include being kept awake at night, being annoyed by people vomiting or urinating and feeling unsafe waiting for public transport (Laslett et al. 2011).

The harms to others resulting from substance use and gambling vary by gender with females reporting more negative harm as a result of knowing drug users than males (Melberg et al. 2011). Healthcare costs include hospitalisations, inpatient and outpatient specialist treatment, general practitioner costs and prescription drug costs (Rehm et al. 2006a). The healthcare costs of the use of addictive substance are immense, with tobacco estimated to cause up to 40% of all hospital illness and alcohol involved in over half of visits to accident and emergency departments in the UK (Nutt et al. 2007). Economic costs refer to lost productivity related to harmful substance use and gambling, for example absenteeism and reduced performance at work (Easton 1997). Law enforcement costs of harmful substance use and gambling are also high, including the cost to society of crimes (such as property loss or damage), policing, criminal charges and incarcerations as well as costs for licensing premises and costs for specialised drug enforcement (Rehm et al. 2006a). Finally, substance use and gambling may result in social care costs, including for substance misuse services and children and families services (Centre for Public Health 2011; Rehm et al. 2009).

2. METHODS

2.1 Definition of a determinant

The disciplines involved in ALICE RAP WA3 approach research differently depending upon the epistemological underpinnings of their subject. For many, use of the term determinants is challenging as they tend to describe factors influencing an outcome or contextual variants of an outcome. In contrast, determinant is often used by other disciplines used in a more literal and deterministic way. Thus, it was important to discuss and develop a definition of determinant which could be applied by all disciplines. During a WA3 meeting the expert panel agreed upon the following definition:

> *"A factor which alone or in combination acts to increase or decrease the likelihood of whether something happens or not. That influence can operate directly or through other factors. For this work package, determinants are used to describe the range of factors at the molecular and cellular, individual, and social environmental levels which, alone or together, increase the likelihood of harmful use. To use the word determinant does not mean that we believe that any of these factors or combination of factors are deterministic in a causal manner."*

2.2 Methods for extracting determinants from the discipline reviews

The model includes each of the determinants identified from analysis of the individual discipline reports on the transition from risky use to harmful use of substances and gambling. Determinants were classified by substance (alcohol, tobacco, cannabis, stimulants, opioids, club drugs and gambling) and level of analysis (cellular and molecular, individual or social and environmental). Following extraction of the determinants from the discipline reviews, an early version of the model was circulated to the WA3 discipline experts to ensure that no determinants had been omitted from the model and that the determinants included were both relevant and themed correctly.

2.3 Barriers to the development of testable models

Our ambition was to use the evidence generated to develop interdisciplinary testable models of addiction. These testable models would illustrate evidenced and hypothesised relationships between different determinants of addiction, providing a road-map for future addiction researchers. However, during the collation of evidence from the disciplines around the determinants of the transition to risky substance use

and gambling, it became evident that developing such testable models would not be possible for two key reasons.

Firstly, there was an absence of evidence. After consideration of the available research pertaining to harmful substance use or gambling we concluded that there is a lack of evidence to support a comprehensive mapping of hypothesised relationships between determinants. Given that lack of supporting evidence, we felt that illustrating these relationships in the model may mislead researchers and policymakers regarding the importance of different determinants and the relationships between them.

Secondly, the diversity of disciplinary approaches to generating evidence around the factors influencing the transition to harmful substance use and gambling has hampered the process of drawing together evidence from across the disciplines. The determinants displayed in Figures 2-9 span a wide range of levels of abstraction, from broad constructs such as institutions of social control to narrowly defined concepts such as features of neurocircuitry. To develop coherent testable models that incorporate such fundamentally different constructs requires the development and nurturing of multidisciplinary relationships that will enable scientific debate around the intricacies of such relationships. Whilst we have initiated such connections over the duration of this project, produce models with greater interactions between determinants and which consider the range of research methods and types of data the disciplines use would require substantially more interaction between researchers.

Given these challenges, we have prioritised utility of the models and have focused on clarity and accessibility for policy makers. At the same time, we have sought to capture and display the full complexity of determinants contributed from all the involved research disciplines involved. The models that we present below do illustrate some of the relationships between determinants by the level of analysis at which they have been included in the model (e.g. molecular and cellular, individual or social environmental) and through the themes under which they have been grouped. Such broad research themes can be used as a guide for further research, highlighting areas for potential multidisciplinary collaboration which would enable us to develop more detailed testable models in the future.

2.4 Key themes in the model

To allow readers to easily interact with the models and rapidly interpret the results, clusters of determinants were arranged into key themes identified by the expert panel. All determinants for each substance were organised within these key themes, with determinants appearing in multiple domains where applicable. The

panel decided to cluster by theme rather than discipline both to highlight the disciplinary overlap between determinants and to encourage engagement from non-specialist audiences and policy makers. Using themes facilitates the quick identification of key messages from our work and may help to target policy responses for different substances.

2.5 Evidencing the model

All determinants within the model are derived from discipline-specific reports written by the expert panel. These reports identify the key evidence on the determinants of the transition from risky to harmful substance use and gambling, and are synthesed within a companion report (Gell et al. 2013). We have not included the citation for each determinant within the model, because it was perceived that this would make the model too cluttered and difficult to read. However, the evidence is presented in tabular format in Appendix 2 (p.82) and within the associated synthesis report (Gell et al. 2013).

2.6 Model validation

To address the challenge of merging synthesising evidence drawn from disciplines with diverse epistemological traditions, we relied particularly on bringing together discipline experts through teleconferences and face-to-face meetings. Such sessions have enabled us to identify challenges and work together to find solutions to emerging problems.

During the development of the model illustrated below we engaged frequently with discipline experts. Experts were consulted regarding which determinants to include and exclude from the model and in the development of key themes in which to cluster determinants. Early versions of the model were circulated to all discipline experts for comment in early January 2014. The lead authors then subsequently contacted each of the disciplines to discuss the models and gather feedback both via teleconference and email. This feedback stimulated discussions around the advantages and limitations of different aspects of the models presented and the suitability of the chosen themes to the different addictive behaviours. Following these initial consultations with discipline experts the models were adapted and a final draft disseminated to all team members for comment and validation at the end of January 2014. All comments were integrated into this final version of the models.

2.7 Methods for the calculation of transition probabilities

2.7.1 General procedure

We identified a large dataset from one European Union member country, where transition probabilities could be modelled. The criteria for selection included a large sample size, representativeness of the general population, young age as many of the transitions to first use in Europe happen early in life (Hibell et al. 2012; Kuntsche et al. 2004; Pitkanen et al. 2005) and a cohort design with as many follow-up points as possible.

2.7.2 EDSP: Dataset description

We identified a German prospective-longitudinal study called Early Developmental Stages of Psychopathology Study (EDSP) for our sample. The EDSP aimed to investigate and describe the course of substance use and related disorders in youth and early adulthood. The design is described in detail elsewhere (Lieb et al. 2000; Wittchen et al. 1998). The study consists of one baseline assessment in 1995 (T0) and three follow-ups. Since the first follow-up comprised only a subsample, we used the second and third follow-up that took place in 1998/1999 (T2) and 2003 to 2005 (T3), respectively.

In 1994 the sample was randomly selected from the population register of Munich and surrounding areas. The age groups 14-15, 16-21, and 22-24 were sampled in a ratio of 4:2:1. Seventy one percent of the initially selected 4,263 people completed the assessment. The resulting sample consists of 3,021 people (49.3% women and 50.7% men) with German citizenship that were 14 to 24 years of age at baseline. Of this baseline sample, 36.2% went to school and 26.4% went to university. Another 19.7% had a job at that point of time and 1.1% were unemployed (Lieb et al. 2000). The majority of the sample were still living with their parents (62.4%) and only a few were married (3.4%). The large majority of participants were part of the middle or upper socioeconomic strata (87.4%). This conforms with socio-demographic features of the region (Lieb et al., 2000). Response rates for T2 and T3 are 84% and 73% of baseline participants respectively (Behrendt et al., 2008). At T2 only 12.8% were still attending school and 36.2% were employed. The proportion of individuals living with their parents decreased to 40.2% and 7.8% were married (Lieb et al., 2000).

Data were assessed using different questionnaires as well as the Computer-Assisted Personal Interview version of the Munich-Composite International Diagnostic Interview (M-CIDI) (Beloch & Wittchen 1997). Validity and reliability of the M-CIDI have been investigated and shown to be satisfactory (Sassi & Development 2010; Zhao et al. 2012). The M-CIDI assesses information about symptoms, syndromes and diagnosis of 48 different mental disorders, as well as information on their onset, duration, and severity in a standardized manner. Both, lifetime and 12-month related questions were applied. The interview section

assessing information on nicotine use and nicotine use disorders was only accomplished when the participant reported that he or she had ever smoked daily for at least four weeks. Information on quantity and frequency of present nicotine consumption, age of onset and offset were assessed, followed by questions concerning abuse and dependence.

In most cases the interview was carried out by psychologists in their psychotherapy training after two weeks of interview training and several practice interviews. Consent was given by the participants or their parents. Most interviews were completed at the participant's home.

2.7.3 Operationalisation: Use, risky use, harmful use, and cessation

In order to calculate transition probabilities we had to work with precise operationalisation rather than broad theoretical concepts. For that purpose we had to modify and in some way reduce the working definitions of our group as shown in Box 1.

Box 1: Working definitions for risky use and harmful use, as defined in Work Area 3.

Risky use

"*All expressions of substance use and gambling, in terms of quantity, frequency, pattern and situational circumstances (e.g. location, time) which are material predictive factors for short- or long-term individual harm, or harm to others including society at large*".

Harmful use

"Substance use or gambling which has caused material harms of social, mental or physical nature which are experienced by the user, other individuals or society at large, where cause means outcomes which would not have occurred without the substance use or gambling".

Looking at nicotine consumption one has first of all to wonder if there is such a thing as risky use that could be differentiated from use and harmful use? DSM-IV does not contain a diagnosis of nicotine abuse, stating that there is no clinical evidence for such a diagnosis (American Psychiatric Association 2000). One could of course describe smoking behaviour as risky when it bears risk for others, e.g. smoking in the presence of others or smoking during pregnancy. Smoking in bed could also be described as risky behaviour since it might be associated with elevated fire hazard. These concepts are not useful for the kind of modelling we conduct here. We therefore excluded risky nicotine use and only looked at abstinence, use, and harmful use. This is of course a major difference within our work compared to the rest of the group. The exclusion of risky use also had practical reasons, since the section was only completed when the interviewee had ever smoked daily for four weeks, making the identification of any less frequent smoking behaviour impossible. Again we

applied two versions: one operationalising harmful use exclusively via dependence and one including a criterion for heavy smoking (at least 20 cigarettes a day). The operationalisations are summarised in Table 1.

Table 1: Operationalisations for abstinence, use, and harmful use, Versions A and B.

	Version A	Version B
Abstinence	No consumption in the past year	
Use	Any consumption	Consumption of a maximum of 19 cigarettes daily
Harmful use	Diagnosis of nicotine dependence	Diagnosis of nicotine dependence or smoking at least 20 cigarettes per day

2.7.4 Operationalisation of age, gender, and comorbidity

In order to have sufficient data for all calculations, we had to focus on major risk factors to include in the model. For reasons described above we decided on gender, age, and comorbidity. Age was split into three groups: 14 to 17, 18 to 22, and 23 to 28. This grouping was made for practical reasons on the on hand, and also because in Germany and most other European countries 18 is the age of legality in relation to smoking. In order to calculate transition probabilities for all these age groups we had to work with baseline as well as the two follow–ups mentioned above. The first two age groups refer to ages at baseline followed up to T2. The last group refers to ages at T2 followed up to T3. This means that the transitions for ages 23 to 28 go back to the same persons as the transitions for the first two age groups. Comorbidity was defined as lifetime comorbidity of any other mental disorder (another substance dependence, an affective disorder, an anxiety disorder, an eating disorder, or a psychotic disorder (assessed only at T2 and T3)), diagnosed in the M-CIDI.

2.7.5 Calculation of transition probabilities

In the first instance, we calculated conditional probabilities of shifting from one status at time A to another status at time B. For example the probability of fulfilling the criteria for harmful use at time C when one was classified as a risky user at time B (see Figure 1).

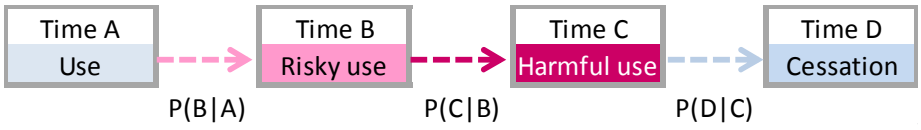


Figure 1: Basic model applied in first calculations

This model does reflect the transitions of major interest within our work, but it does not satisfactorily reflect reality. The model in Figure 2 does not take into account that only a fraction of people do conform to the theoretical model of progression from use to risky use to harmful use and so on. Also the delay of three to four years makes it impossible to follow each person as precisely or as closely as desirable. Even if a person passed through a phase of risky use between use and harmful use, it is possible to miss that phase somewhere in the delay of several years.

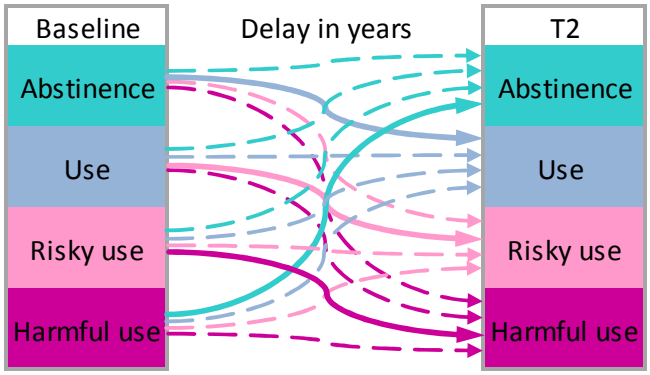


Figure 2: Transition model applied in final calculations.

Two things changed in the second step in order to depict the ongoing processes entirely and more precisely: abstinence was included in the model and each possible transition was calculated separately as shown in Figure 2. Transition probabilities were calculated for each subgroup (2 genders x 2 values of comorbidity x 3 age groups). The twelve resulting groups each contained the four patterns of use, leading to twelve transitions to another category of use to be calculated in each group. Of course in each subgroup a fraction of persons stayed within one category of use from baseline to T2 (or T2 to T3, respectively). The transition probability is the probability that a person is in use category B at time 2 given he/she was in use category A at time 1. In other words it is the number of people who switched from use category A at time 1 to use category B at time 2, divided by the total number of people in use category A at time 1. Considering the multitude of transitions combined with partially small Ns in each group, we decided not to calculate logistic regressions. All transition probabilities were weighted in order to account for age-stratification in sampling as well as age, gender, and regional differences in response rates at baseline. So far, no measurement errors have been taken into account and no confidence intervals calculated. This will be done in further analyses. All calculations were performed using STATA 12.

2.7.6 From transition probability to annual rate

The calculated transition probabilities depend on the delay between the two times of assessment. Logically the number of people (and thereby the transition probability) switching from one consumption category to another is larger when we observe people for several years instead of just a few months. We consequently

broke down the calculated transition probabilities to annual rates with respect to the group-specific delay between the assessments. We calculated rates per year in Excel based on the formula:

$$\sqrt[n]{\quad}$$

n= Group specific delay in years
P(B|A) = Calculated transition probability in %

2.7.7 Simulation

Based on the calculated annual rates we started simulating the course of prevalence during youth and young adulthood (age 14 to 30) for 100,000 fictitious people in each of four groups: females with no comorbidity, females with comorbidity, males with no comorbidity, and males with comorbidity. As a starting value at age 13 we took prevalence for use and abstinence from the German subsample in the ESPAD report (Hibell et al., 2012). We applied the calculated annual rates in the following manner: for each consumption pattern it was calculated how many people changed to other consumption patterns and how many people joined the respective consumption pattern from other consumption patterns within one year. For example in order to calculate the number of users in year X, we took the number of users in the preceding year X-1 and subtracted the people switching to abstinence (annual transition probability from use to abstinence multiplied by the number users in year X-1) or harmful use. Then we added the people that switched into the category user from other patterns of use in the preceding year (annual transition probability from abstinence to use multiplied by the number of abstinent people in year X-1 and so on). The results were then used to calculate the simulated N in the next year and so forth. For each age group the respective annual transition rates were used, leading to four gender- and comorbidity-specific models, each containing transition probabilities for three different age groups. These simulations were calculated using Excel.

3. RESULTS

3.1 The models

A series of models illustrating the determinants identified by each discipline was constructed covering a range of addictive behaviours separately including alcohol, tobacco, cannabis, stimulants, opioids, club drugs and gambling. The models are displayed below (p.211-277). The substance to which each map refers appears in the top left hand corner of the page. Within these substance-specific models the determinants are grouped by level of analysis (molecular and cellular, individual, and social environmental), with each level of analysis distinguished by different background shading and a legend down the left-hand side of the model. The base of this model represents the molecular and cellular focus, the middle layer represents the individual focus, and the top, darkest layer represents determinants with asocial environmental focus.

Within the model, determinants are grouped according to different expert-agreed themes within each level of analysis (see Section 2.3, p.12). At the molecular and cellular level the themes identified are 'Impact on and/or Dysregulated Neurocircuitry', 'Impact on and/or Dysregulated Neurotransmitters' and 'Drug Kinetics'. At the individual level the themes identified are 'Consumption', 'Emotional and Cognitive Processes' and 'Life Circumstances'. At the social environmental level of analysis the themes identified are 'Marketing and Availability', 'Social and Cultural Norms', 'Social Control', 'Power and Social Status' and 'Environment of Use'. Those determinants which influence multiple themes appear once in each of the themes where they exert effect, for example within the alcohol model (Figure 3, p.21) 'stigmatisation' can be found within both 'Social and Cultural Norms' and 'Social Control'.

The gambling model presents an additional theme of 'Structural and Situational Characteristics of Gambling Activities', which is used to describe elements of the gambling activity including the speed of the game and the size of the jackpot. This theme does not fit within the model structure used for harmful substance use and is therefore included in the gambling model outside of the three levels of analysis that structure the substance use models (Figure 9, p.27).

We now present each of the substance specific models followed by a brief description of the meaning and content of each expert-agreed theme.

Figure 3: the alcohol model

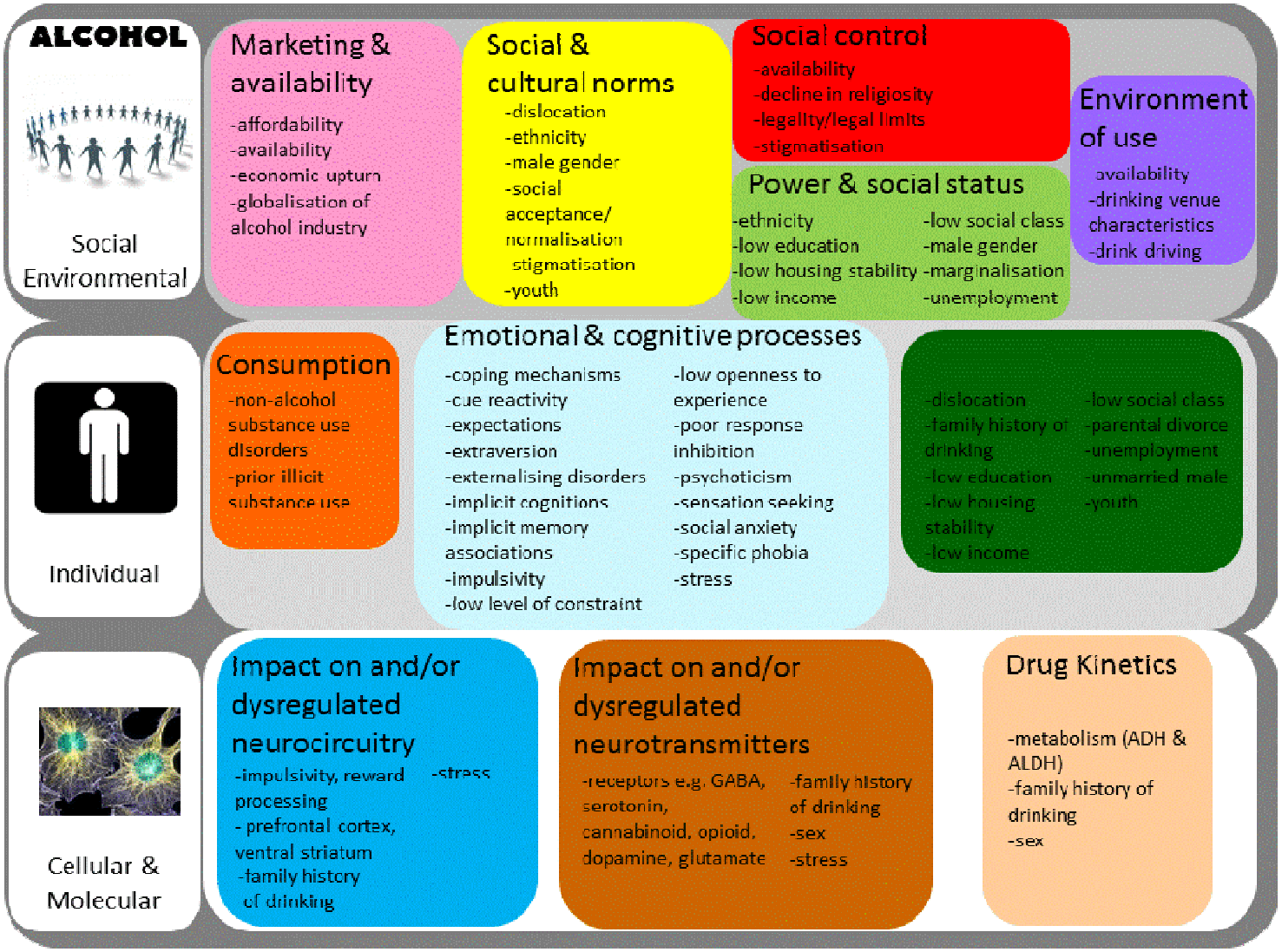


Figure 4: the tobacco model

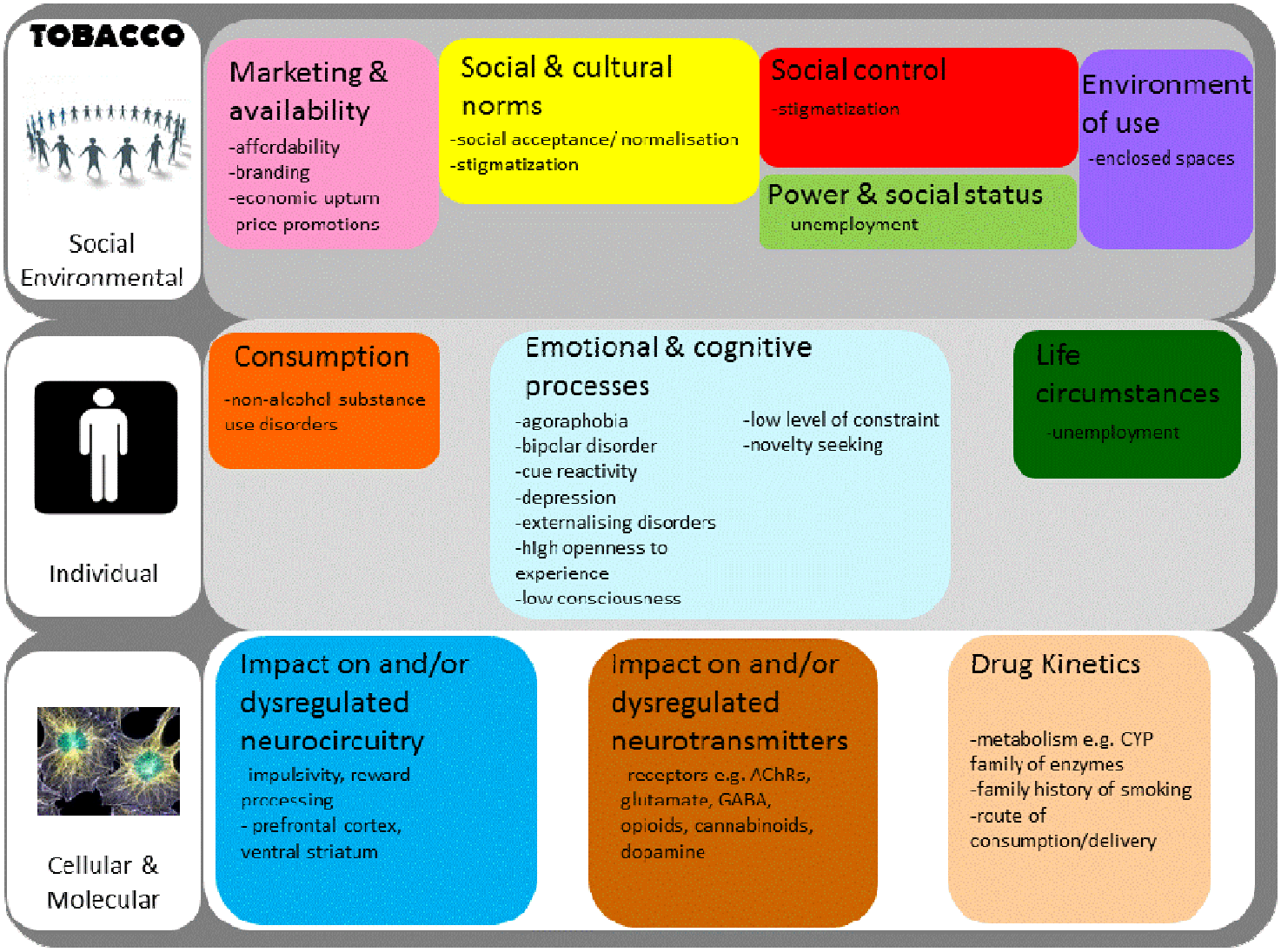


Figure 5: the cannabis model

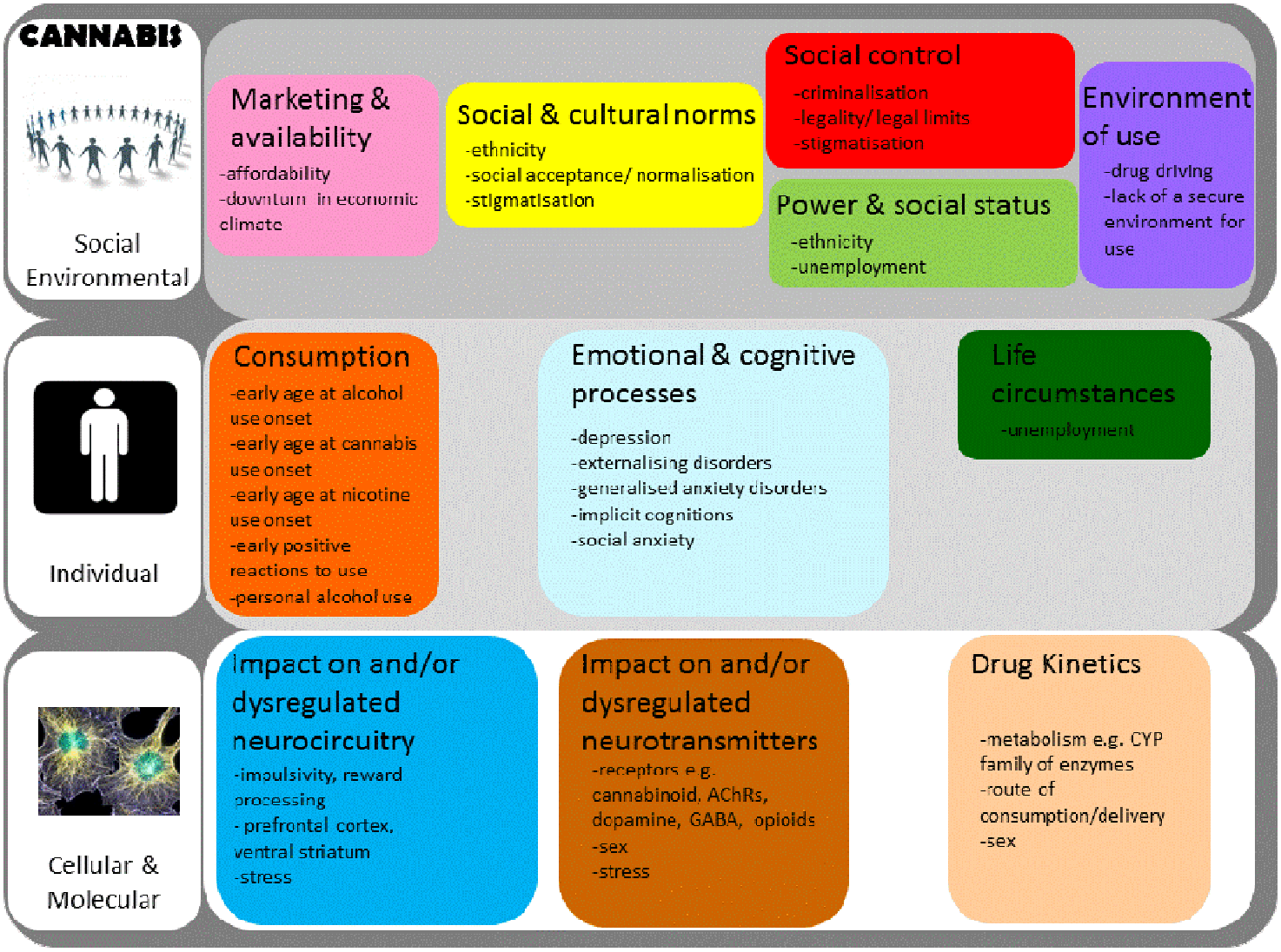


Figure 6: the stimulants model

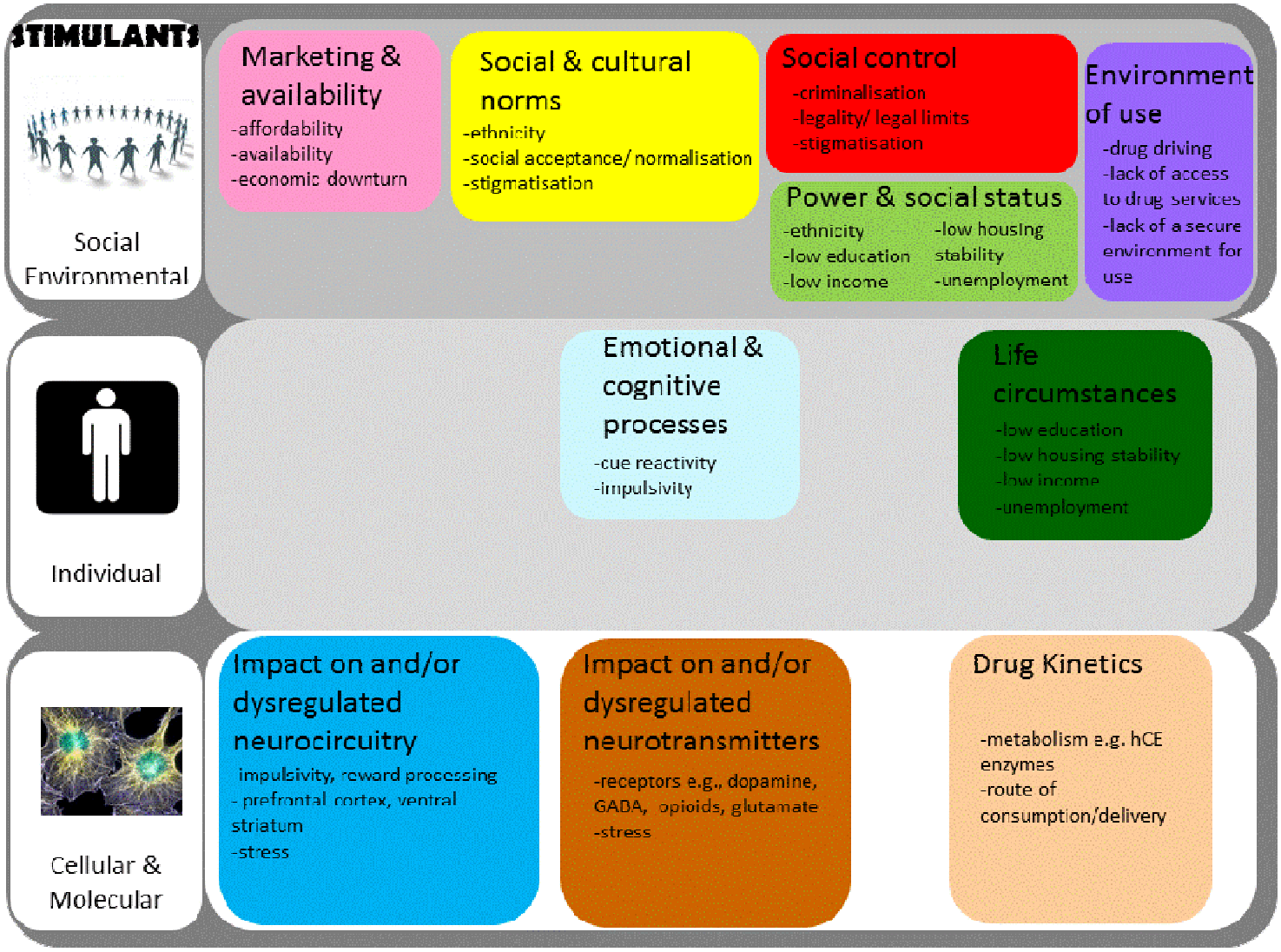


Figure 7: the opioids model

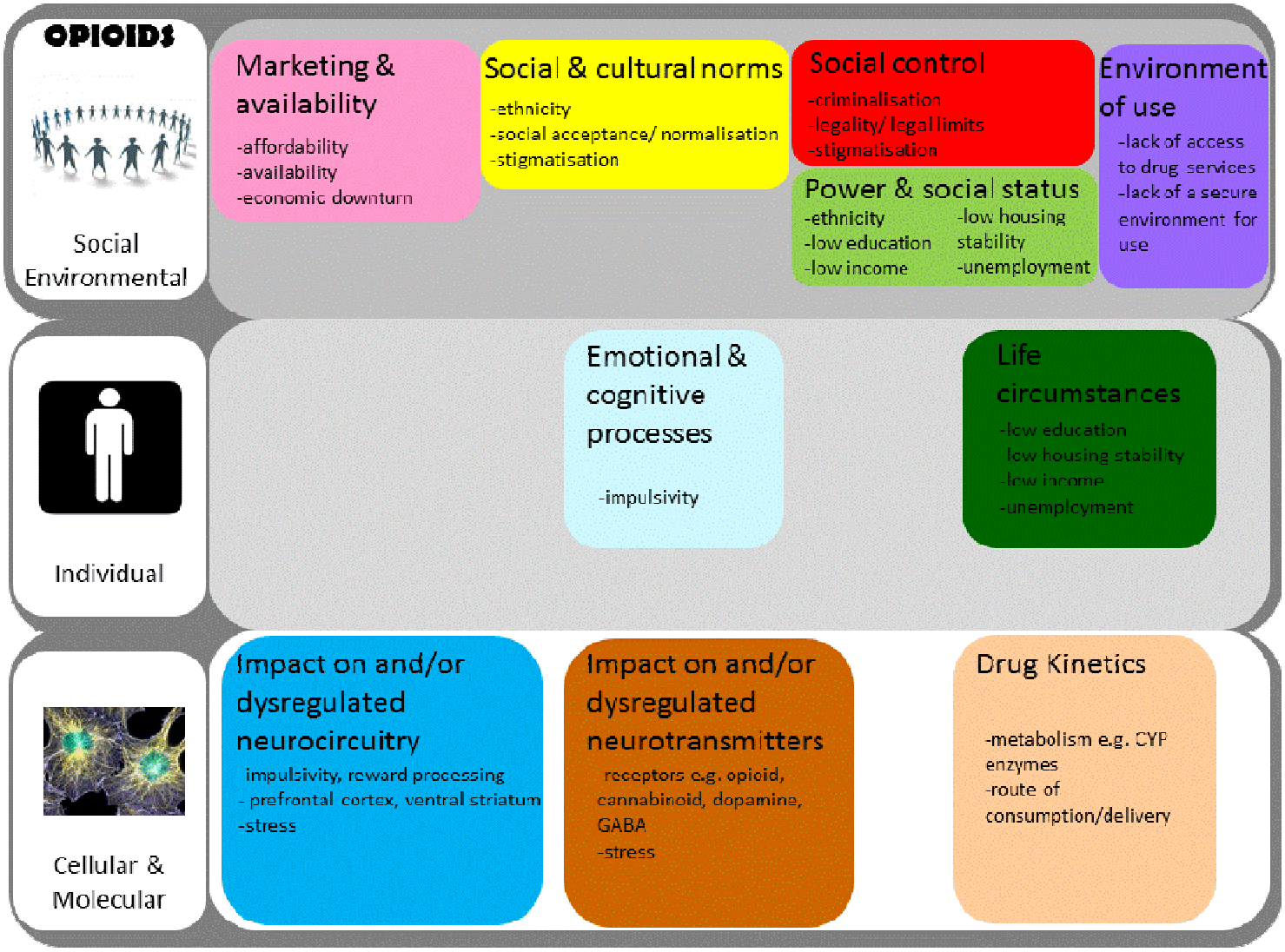


Figure 8: the 'club drugs' model

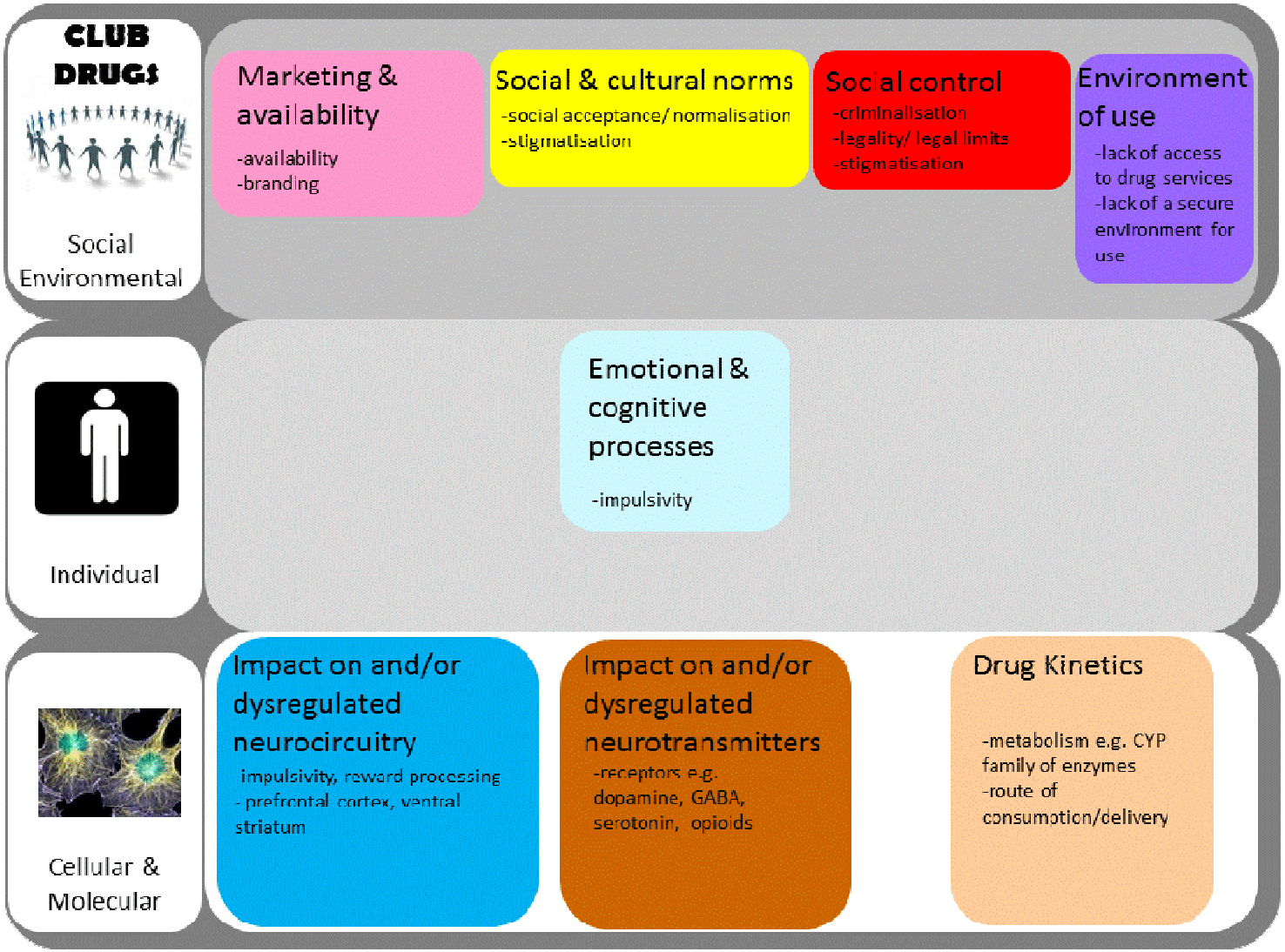
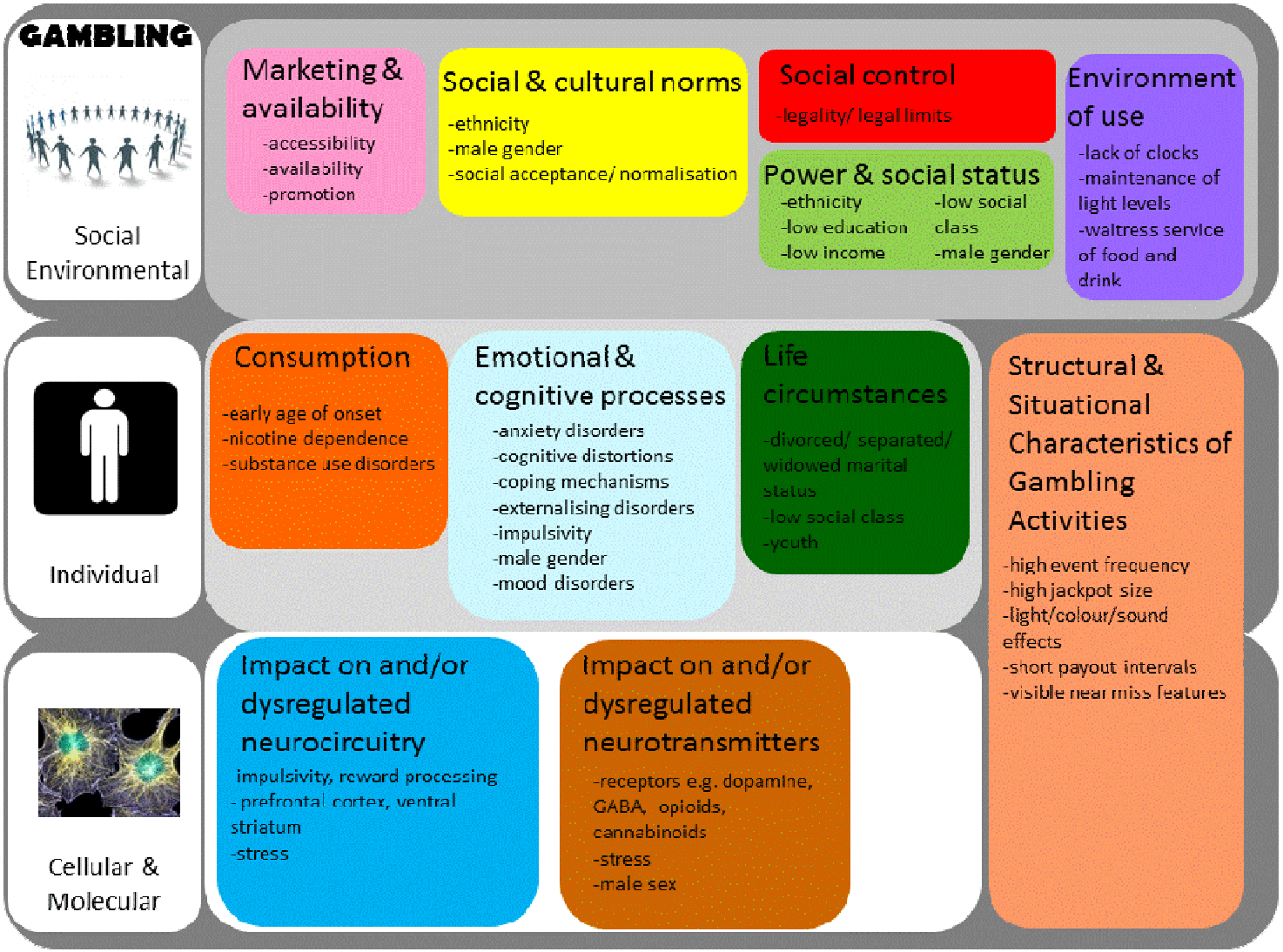


Figure 9: the gambling model



3.1.1 Marketing and Availability

Harmful use here is largely concerned with an individual's access and economic power in relation to purchasing a product (e.g. a substance or gambling activity). Consequently, for legal substances such as alcohol and tobacco, determinants in this theme often refer to the spending power of the individual, with factors such as an economic upturn and price promotions resulting in the individual having more money available for purchasing addictive substances, with a potential knock-on effect on levels of harm (Figure 3, alcohol & Figure 4, tobacco, p.21-22) (Cawley & Ruhm 2011; Ettner 1997; Pacula 2011; Ruhm & Black 2002; World Health Organisation 2012; Xu & Kaestner 2010)).

Conversely, greater harm is derived from the illegal substances in periods of economic downturn (e.g. Figure 5, cannabis, p.23). Different mechanisms are in action for the different substances. For example, for cannabis use in an economic downturn may lead to unemployment which increases an individual's free time available for substance use (Arkes 2007; Chalmers & Ritter 2011; Henkel 2011). For opioid users, economic constraints during periods of economic downturn can result in harmful behaviour as users may switch to more harmful routes of administration, such as injection to increase the bioavailability of the drug (Figure 7, opioids, p.25) (Ben & Bastianic 2011). An economic downturn may increase the experience of stress and increased use of a substance may be used as a coping mechanism (Arkes 2007). Finally, during periods of economic downturn, factors including constrained law enforcement budgets, reduced drug prices, reduced dealer wages and increases in the number of drug dealers (resulting from increases in unemployment), combine to increase the availability and affordability of illicit substances (e.g. Figure 6, stimulants, p.24), with the associated increased consumption resulting in increased harm (Bretteville-Jensen 2011).

3.1.2 Social and Cultural Norms

Societies have implicit and explicit rules about how members of that society should behave as individuals and towards others. Thus, within different societies there may be different levels of acceptance around behaviours, such as particular patterns of alcohol consumption, use of cannabis, and gambling activities. The degree of social acceptance surrounding substance use and gambling may influence the level at which an individual engages in addictive behaviours and, where use is considered normal behaviour for a given subgroup of the population; this may increase the exposure of an individual to harm. For example, it is normative within the UK for young adults to engage in binge drinking even though this pattern of use has been linked to a range of acute harms (Hallgren et al. 2012; Rehm et al. 2012; Rehm et al. 2005; Room 2001; Skog 1985). Social acceptability of binge drinking in this age group may also persuade individuals to engage in such levels of drinking to meet normative expectations of their peers. Young adults typically 'mature out' of this pattern of consumption as they grow older; however we do see high levels of alcohol consumption in

older age groups across many European countries. The extent of this behaviour serves to normalise it within certain subpopulations and the resultant increase in alcohol consumption levels impacts in turn upon levels of chronic alcohol-related harms, such as liver cirrhosis.

Population subgroups may experience greater levels of harm as a result of culturally-specific patterns of behaviour. For example, some ethnic groups show an increased risk of harmful behaviour (e.g. Figure 9, gambling, p.27). Such differences are often explained by socioeconomic factors such as lower income among the minority groups, but it has also been suggested that the acceptability and accessibility of certain substances within these groups may influence harmful use (Levine & Small 2007; Schrager et al. 1991; Welte et al. 2004a; Welte et al. 2004b). Dislocation theory suggests that individuals who are displaced or leave their traditional culture may be at increased risk of engagement in harmful substance use and Alexander (2008) describes a number of examples where groups of individuals may use a substance (such as alcohol) to cope with the challenges of living in a foreign environment and society.

3.1.3 Social Control

Society aims to prevent harmful substance use and gambling to ensure the safety and longevity of its members. A number of mechanisms are employed to modify certain undesirable behaviours, including legislation (e.g. to ban substances perceived to be harmful to individuals or society or to restrict use below a certain age) and regulation (e.g. to monitor production of certain substances). For example, the use of alcohol and tobacco and engagement with gambling activities is restricted, usually at the point of purchase, for those under eighteen years of age across the majority of Europe (NHMRC 2009; Room 2004a; Room 2004b). Those aged less than 18 years are considered unable to rationally balance the harm and benefits of these behaviours. Additionally, the substance use may have greater harm potential at younger ages. For example, the potential harm to the brain of drinking alcohol is higher at younger ages compared with after it has fully developed (Jain & Balhara 2010).

Some substances are subject to strict prohibitions because any use is considered harmful, for example cocaine and opioids. Individuals caught selling or possessing such substances may be subject to criminal sanctions (such as a monetary fine or imprisonment). However, such criminalisation of behaviour can directly harm individuals (e.g. Figure 7, opioids, p.25) in a way which might not exist in a comparable society where the substance held a licit status. This is because individuals with a criminal status may be stigmatized by or marginalised from society, struggle to gain employment, and find their options for living arrangements limited (for example low income housing estates with potentially high levels of illicit drug use, thus perpetuating the situation) (Stover & Michels 2010).

In addition to explicit Government-based legal and regulatory controls, society may exert control through implicit or non-Governmental means (e.g. stigmatising certain behaviours or religious beliefs and injunctions). The decline in religiosity has been cited as one determinant of increased harm from alcohol (Figure 3, alcohol, p.21), with the reduction in moral restrictions a potential factor influencing harmful substance use. Another example of gradual societal change in perceptions surrounding addictive substance use is the reduction in stigma surrounding the use of cannabis which has reduced the potential for social harm to the individual (e.g. Figure 5, cannabis, p.23) (Conrad 1992; Conrad & Schneider 1980).

3.1.4 Power and Social Status

Across all the models, the determinants within the theme of power and social status include; unemployment, low income, low education, low housing stability, lower socioeconomic status, male gender and ethnicity. These determinants reflect that a lack of power and low social status are determinants of harmful drug use and gambling.

Traditionally, an increased level of stigma has been associated with females taking part in these activities (Gomberg 1988; McGowan 2003) and thus has often deterred their involvement. Increasing gender equality is however having an influence on the number of women who engage in harmful drinking behaviours (Bloomfield et al. 2006; Kuntsche et al. 2006; Makela 1999; Meng et al. 2013; Pearson 1996), which highlights that determinants have an unstable degree of influence on behaviours over time.

It is interesting to note that the theme of power and social status is absent from the club drugs model (Figure 8, p.26), suggesting that an individual's position within society is not an important factor in the harmful use of club drugs.

3.1.5 Environment of Use

The environment in which a behaviour takes place can affect whether the behaviour is in itself harmful. Studies have shown that venue characteristics such as a permissive environment, discounted drinks promotions, poor cleanliness, crowding, loud music and poor staff practice are all factors associated with harmful drinking (Figure 3, p.21) (Hughes et al. 2011; Stead et al. 2012). In gambling studies the casino environment has been found to influence levels of harm due to, for example, designing the environment such that the absence of clocks and the maintenance of light levels prevent awareness of time passing and serve to maintain gamblers' engagement with the game. Additionally, gamblers may be served food and

drink at the tableside so that they do not leave the game so often and continue to gamble for longer periods of time (Griffiths 2009).

Over recent years strict regulations have been introduced relating to the environments in which smoking is permitted. In many countries it is now illegal to smoke in public places, a policy introduced to minimise harms of second hand smoke and in recognition that smoking in enclosed spaces increases the inhalation of toxic compounds, thus resulting in increased harm (England Department of Health 2011; Epicentro 2013). For illicit substances the lack of a secure environment in which to take drugs can increase harm. The illicit nature of such drugs results in users being restricted in where they can use the drugs to avoid criminal sanctions. This often leads to drug users inhabiting areas which are less visible, and thus putting themselves at an increased risk of violence (Coumans et al. 2006; Dahl 2008b). Similarly, the illegal status of many drugs results in harm to the user by the lack of access to drug services, such as needle exchanges and street level nursing (Bourgois et al. 1997a; Burris et al. 2004; Castro & Singer 2004).

Drug driving is a determinant of harm for alcohol, cannabis and stimulants, as research shows that driving under the influence of these substances is related to an increased number of road traffic accidents (Ramaekers et al. 2000; Stoduto et al. 2012).

3.1.6 Consumption

The manner in which an individual consumes a substance or whether it is consumed alongside other substances may give rise to harm. For example, an individual who has a non-alcohol substance use disorder has an increased likelihood to engage in harmful alcohol and/or tobacco consumption (Figures 3 & 4, p.21-22) (Behrendt et al. 2011). Additionally, the prior use of illicit substances increases the likelihood of an individual engaging in harmful alcohol use (Swendsen et al. 2010). These factors may operate through individual normalisation of high-level consumption of alcohol or nicotine, as their perception of moderate use may be skewed by their prior problematic substance use. Alternatively, alcohol or nicotine may be used as a substitution during attempts to quit a different substance, and this may lead to harmful consumption of these drugs in an attempt to overcome cravings for the original substance (Caulkins & Nicosia 2010).

Harmful cannabis use may be influenced by an individual's personal use of alcohol (Figure 5, p.23), as these substances have been shown to be complementary with the use of one potentially resulting in higher use of the other (Caulkins & Nicosia 2010). Additionally, the age of onset of alcohol, tobacco or cannabis use may be an influential factor related to harmful cannabis use, with a younger age of onset associated with increased risk of harmful cannabis use later (Behrendt et al. 2011; Schaub et al. 2010).

An association has been found between harmful gambling and a range of substance misuse behaviours or gambling behaviours (Figure 9, p.27). This includes nicotine dependence, substance use disorders (Lorains et al. 2011) and an early age of onset of gambling (Johansson 2006; Petry et al. 2005; Volberg et al. 2001). Operationalisation of these determinants is purported to be related to the lack of risk awareness in young people, the expansion of social networks of gamblers, habit formation and the normalisation of addictive behaviours through exposure to and membership of subcultures(Becker 1963; Caulkins & Nicosia 2010; MacDonald 2004; Measham et al. 1994).

No determinants were highlighted within this theme for the substances of stimulants, opioids or club drugs, (Figures 6-8, p.24-26) reflecting the reduced understanding we have of these behaviours.

3.1.7 Emotional and Cognitive Processes

Our disciplinary experts identified emotional and cognitive processes as another key theme. This theme considers individual thought patterns, which may increase the likelihood of engaging in harmful substance use or gambling. For example, problems such as externalising disorders, mood disorders and anxiety disorders may result in disordered thinking, and personality traits such as impulsivity and extraversion may contribute to engagement in harmful behaviours.

Trait impulsivity is associated with low levels of constraint, novelty seeking, sensation seeking and poor response inhibition, which may cause an individual to engage in an activity such as harmful substance use or gambling without processing the significance of such actions. Thus, impulsive individuals may make the decision to act before they are fully aware of the possible consequences (e.g. Figure 1, alcohol, p.21) (Chambers & Potenza 2003; Elkins et al. 2006; Garavan & Weierstall 2012; Nigg et al. 2006; Sher et al. 2000; Verdejo-Garcia et al. 2008; von et al. 2008). Related to impulsivity is high cue reactivity, where images associated with substance use or gambling increase the craving and appetite to engage in a behaviour, and cause an individual to engage in rapid habit-type decisions without full appreciation of the effects.

Research shows that externalising disorders such as attention deficit hyperactivity disorder (ADHD) may increase the likelihood of engaging in harmful substance use through the same impulsive pathways (Elkins et al. 2006; King et al. 2004; MacDonald 2004). Mood disorders, anxiety disorders and phobias, such as agoraphobia, may also influence engagement in harmful substance use and gambling through a different pathway; namely the use of substances as a coping mechanism (Huizink et al. 2006; Serena et al. 2004).

The alcohol model is the most densely populated of those presented here and this is likely the result of the greater amount of research in this field over a long time period. It also partly reflects the expertise of our panel in this area. Conversely, illicit substances including stimulants, opioids and club drugs show relatively few determinants within this domain (Figures 6-8, p.24-26). This may be related to their illicit nature which makes them more challenging to study.

3.1.8 Life Circumstances

An individual's life circumstances may influence their engagement in harmful substance use and gambling, for example through increased opportunity or the use of a substance as a coping mechanism during challenging times. Determinants in this theme are broadly associated with the level of stress or hardship experienced by the individual, such as unemployment, lower socioeconomic status, low income and housing instability (Figures 6 & 7, stimulants & opioids, p.24-25). Additionally, as a result of factors such as unemployment, individuals may have greater opportunity to engage in harmful behaviours through social networks and leisure time (Schrager et al. 1991; Van Ness et al. 2004). Similarly mechanisms have been proposed for gambling behaviour among divorced/separated/widowed people (Figure 9, p.27), with gambling used as both a coping strategy and use increasing as a result of fewer restrictions on behavioural choices (Hodgins et al. 2011; Petry et al. 2005).

Once again, the model for club drugs is absent of determinants in the theme of life circumstances, reflecting our lack of knowledge surrounding the harmful use of such substances (Figure 8, p.26).

3.1.9 Impact on and/or Dysregulated Neurocircuitry

When an individual engages with substance use or gambling their neurocircuitry becomes altered, giving rise to an increased desire to repeatedly engage in such activities and ultimately leading to habit formation and feelings of compulsion. The brain regions of the ventral striatum and prefrontal cortex are important in the processing of reward and cognitive control respectfully, and thus dysregulation within these two regions can lead to harmful substance use and gambling (e.g. Figure 3, alcohol, p.21) (Bechara 2005; Goldstein & Volkow 2011; Koob & Volkow 2010a; Verdejo-Garcia & Bechara 2009). It is hypothesised that changes in the neurocircuitry associated with addiction result in reduced activity within the ventral striatum whilst an individual is anticipating taking a drug, with changes in this region following consumption that give rise to reward sensations (Everitt & Robbins 2005; Knutson & Bossaerts 2007; Robinson & Berridge 2003). However, the results of neuroimaging studies are variable (Bjork et al. 2012; Garavan & Weierstall 2012; Nestor et al. 2010; Wrase et al. 2007). Areas within the prefrontal cortex are implicit in impulse control, with greater impulsivity involved in the vulnerability to drug addiction, particularly stimulants (Schoenbaum et al. 2006).

Additionally, stress is a determinant of harmful use, with many patients citing stress as the reason for their harmful substance use or gambling; the relationship between alcohol and stress is particularly well researched. Prolonged substance use causes neural changes which mirror stress responses (Kiefer & Wiedemann 2004; Sinha 2009). These adaptations are may be overcome upon administration of the substance, reducing the individual's feelings of stress and thus driving repeat behaviour during future episodes of stress (Adinoff et al. 1998; Kiefer & Wiedemann 2004; Koob & Moal 1997; Koob & Volkow 2010b; Sinha 2009; Walter et al. 2013; Wand & Dobs 1991). Further, stressful life events can incite changes to neurocircuitry. Stressors in the early years have been shown to result in changes within the brain systems involved in depression, anxiety and substance use disorders (De Bellis et al. 1999; Heim et al. 2001) and experiments within non-human primates show maternal separation at a young age increases stress responses and alcohol consumption in such animals (Higley et al. 1991). Addicts are 'hyper-sensitive' to stress due to brain adaptations from prior substance use, and therefore the response following administration of a substance is often calm, increasing the likelihood of them engaging in repeated harmful behaviour to moderate such feelings (Langleben et al. 2008; Mei et al. 2010; Sinha 2007; Sinha & Li 2007).

3.1.10 Impact on and/or Dysregulated Neurotransmitters

The levels of different neurotransmitters and receptors within the brain are carefully balanced to allow correct functioning. Engagement in substance use and gambling leads to alterations in these delicate balances as the brain adapts to either the chemical changes that the different substances impose upon it or the thought processes and bodily changes which are associated with taking part in gambling. For example, a reduction in dopamine receptor availability and release is associated with the transition from risky to harmful stimulant use (Figure 6, p.24) (Volkow et al. 2004) and an increase in opioid receptors was noted in recently abstinent opiate addicts (Figure 5, p.25)(Williams et al. 2007). These adaptations are associated with cravings and feelings of compulsion within the user and thus drive repeated use (Goldstein & Volkow 2011; Leyton 2007; Robinson & Berridge 1993; Robinson & Berridge 2003). Beyond substance related adaptations, some individuals may carry polymorphisms in neurotransmitters such as the dopamine receptors which result in low level of expression and as such promote similar craving and compulsive behaviour following exposure to such substance or gambling (Agrawal & Lynskey 2008; Agrawal et al. 2012).

3.1.11 Drug Kinetics

Different enzymes have different metabolic rates within the body to process different substances. For example, a version of the ALDH2 gene, which some people of East Asian origin may carry, is defective and results in the build-up of a toxic intermediate in alcohol metabolism (Figure 3, alcohol, p.21) (Ball 2004;

Edenberg & Foroud 2006; Gizer et al. 2011; Kim 2009; Kuo et al. 2008; Reich et al. 1998). This gives rise to flushing and feelings of dizziness in people who carry this gene. The CYP family of enzymes are important in smoking of tobacco and cannabis as they metabolise nicotine and increase the liking of such substances (e.g. Figure 4, tobacco, p.22) (Lee et al. 2010). The CE enzymes metabolise stimulants and different enzymatic rates may increase or decrease the effects and therefore the likelihood of an individual repeatedly engaging with, or increasing their use of, these substances (Kamendulis et al. 1996). The route of drug delivery and mode of use is important in metabolism as smoking is known to deliver a rapid 'hit', as does injection of drugs, as these rapidly enter the bloodstream, whereas oral consumption has a much slower effect. This can be both more dangerous in that an individual may ingest a larger amount of the substance prior to its effects being felt and so may overdose without knowledge, or safer as the large 'hits' delivered by injection may be too rapid for the body's systems to cope with.

No determinants are listed for the kinetics of gambling (e.g. metabolic changes at the biological level), as this is not an ingested substance. Instead, we have introduced the separate theme of structural and situational characteristics of gambling activities to reflect the potential influence of the activity itself on harmful use.

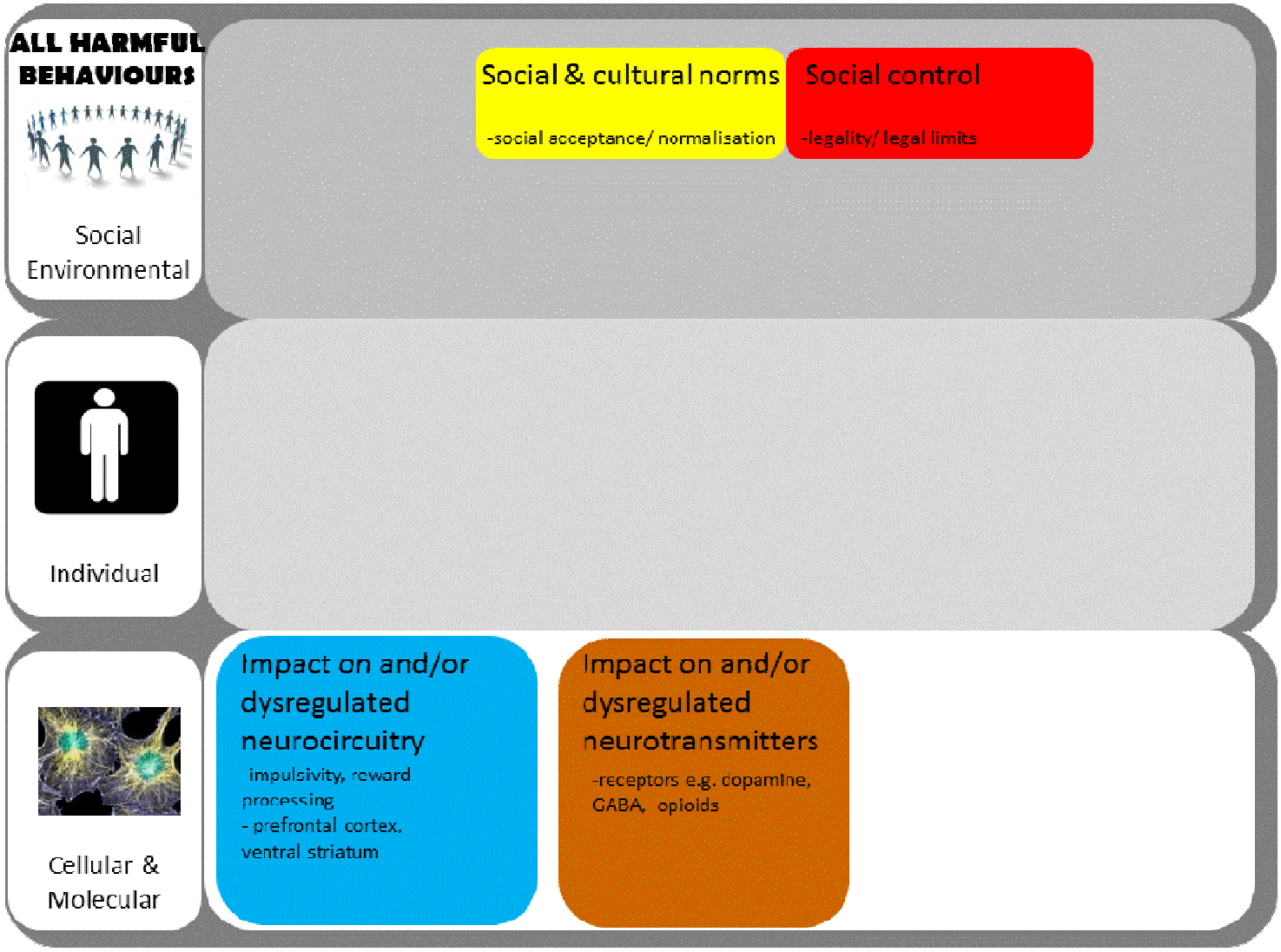
3.1.12 Structural and Situational Characteristics of Gambling Activities

Not all forms of gambling are the same, for instance, playing the national lottery once a week is very different to gambling on a fruit machine. The structural characteristics of the gambling activity have been shown to be important in the maintenance of gambling behaviours and may exacerbate such behaviours to harmful levels (Grifftihs 1993; Parke & Griffiths 2006). Indeed it has been suggested that the structural characteristics of games, such as fruit machines, have the potential to induce excessive gambling regardless of an individual's innate tendencies (Grifftihs 1993; Parke & Griffiths 2006). As such the game characteristics may be seen as comparable to drug characteristics or drug kinetics, where drugs that show a rapid action appear to be more addictive than those which are slower. The structural characteristics of the game appear to influence the relative addictiveness of the activity, with games that have a high event frequency and short payout intervals with a high jackpot size showing a greater capacity for harmful use.

3.2 Determinants common to multiple substances

Whilst it is evident from Figures 3-9 that there are many differences in the determinants of harmful use of different substances and gambling, we have identified some determinants that are common to all harmful behaviours. In Figure 10 we present these determinants common to multiple addictive behaviours.

Figure 10: determinants common to multiple substances



At the cellular and molecular level the majority of the determinants within the themes of 'Impact on and/or dysregulated neurocircuitry' and 'Impact on and/or dysregulated neurotransmitters' are similar across all the addictive behaviours examined here. This demonstrates that the majority of the substances' neurological effects converge on common pathways and transmitters of the brain, such as the mesolimbic (reward) pathway, and other dopaminergic pathways of the brain (Agrawal & Lynskey 2008; Agrawal et al. 2012; Di Chiara & Imperato 1988; Everitt & Robbins 2005; Koob & Moal 1997; Nestler 2005; Robinson & Berridge 1993; Volkow & Muenke 2012). In contrast, the theme of 'Drug Kinetics' is absent from Figure 9, in all likelihood because of the specific nature of this theme; 'Drug kinetics' refers only to harmful substance use, and is irrelevant to gambling as this activity does not require the ingestion of a substance. Considering the addictive substances examined within our work only, we can see that an individual's metabolism is a common determinant of harmful substance use, with some individuals able to inherently process such substances in less harmful manners without the build-up of toxic intermediates. Equally the route or method of substance consumption is a determinant for all substances excluding alcohol, (which almost exclusively ingested and so the route of consumption does not vary), and can increase the harm both through increased bioavailability of a drug which may damage bodily systems and associated risks such as increased risk of disease from injection over smoking drugs. We propose that such common determinants of harmful substance use may provide useful targets for initial policy strategies for tackling harmful substance use.

It is interesting to note that we have been unable to identify any common determinants at the individual level of analysis. This partly reflects different modes of use of each substance (and gambling). Most of the models reflect the determinant impulsivity within the theme 'Emotional and Cognitive Processes', however, this is absent from the tobacco and cannabis models. Within the tobacco model the determinant novelty seeking is displayed, which is a component of impulsivity, but impulsivity is not a determinant in itself. This illustrates the variance in research processes and terminology used by researchers across the different disciplines represented within our work. For cannabis, there is insufficient evidence to support an association between impulsivity and harmful use. This may be related to both the psychopharmacologic effects of the substance and the position of this substance within modern societies, which does not meet users' desires in traits such as sensation seeking (ASHTON 2001). Whilst we have been unable to identify any common determinants within our research, this may reflect an absence of research rather than that there are no individual level determinants common to all the substances and gambling.

At the social environmental level of analysis the determinants which are common to the harmful use of all substances and gambling are from two different themes; 'Social and Cultural Norms' and 'Social Control'. The determinant social acceptance/normalisation is relevant to harmful use of each of the substances as

increased social acceptance and normalisation of substance use or gambling within a society may promote harmful use of a behaviour. Equally, the lack of social acceptance may influence the harmful use of substances as individuals lack awareness and the necessary provisions to allow safe use, for example the use of needle exchanges and street level nursing (Bourgois et al. 1997b; Burris et al. 2004; Castro & Singer 2004; Coumans et al. 2006; Dahl 2008b). Similarly, the legal status of an activity may influence the harm resulting from substance use or gambling, with alcohol, tobacco and gambling being perceived as safer than illicit substances due to their legal status (Nutt 2012). This may result in a lack of understanding of the risks of use leading to individuals suffering harm from legal substances. Conversely, the illegality of certain substances may drive harm through 1) improper controls (e.g. monitoring of substance content) 2) the imposition of punitive sanctions and criminalisation of the individual 3) the creation of illicit markets and 4) the withholding of protective measures (such as needle exchange facilities) (Rolles 2010).

The limited number of common determinants identified for the harmful use of substances and gambling indicates the diversity of research focus on different addictive behaviours and the plethora of motivations underlying use by individuals in different societies. This highlights the importance of continuing to research individual substances and behaviour separately in order to optimally target and address the determinants of addictive behaviours, rather than treat all addictive behaviours as one common problem with common underlying causes.

3.3 Multidisciplinarity within the model

Research within the addiction field has long been fractured, with knowledge from across the disciplines being brought together all too rarely. It has been compared to 'The tale of the elephant and the blind men', where each man touches and describes one part of the animal, but none can describe the whole beast. ALICE RAP seeks to advance multidisciplinary addiction research and our models highlight potential areas for work which can improve our current understanding and highlight new solutions to societal problems.

One key challenge in developing a model for harmful substance use and gambling was illustrating the state of knowledge. In presenting the model clustered around themes, we have masked some of the additional learning around the multidisciplinarity of research of the determinants of risky substance use and gambling. As such, here we present an alternative version of the model, targeted towards researchers and policy makers with an interest in the multidisciplinarity of research on risky substance use and gambling.

3.3.1 Example: the multidisciplinarity of alcohol research

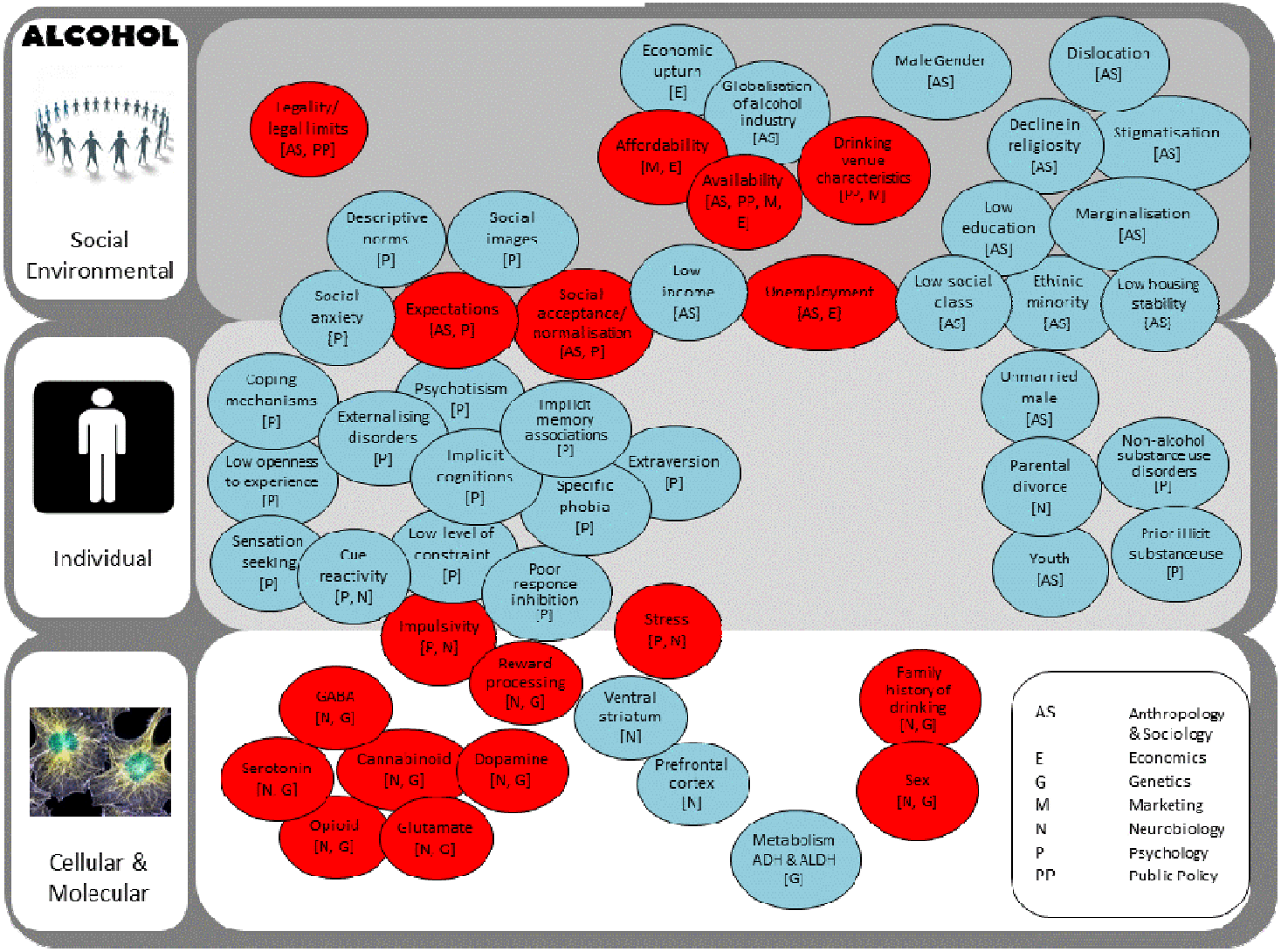
Figure 11 (p.40) presents a variation on the alcohol model described in Section 3.1 (p.21) (for another example see Appendix 3: stimulants model with multidisciplinary emphasis, p.90). The same determinants are illustrated within both models, but rather than clustering determinants into broader themes, each determinant is a stand-alone bubble in Figure 11. The lighter, blue circles indicate determinants that are researched by a single discipline whilst the darker, red circles show determinants that are researched within two or more disciplines. Within each circle, the square brackets indicate the disciplines that have contributed to research on that determinant.

The model illustrates that approximately one-third of the determinants of harmful alcohol use were researched by at least two disciplines, with half of these showing overlap between neurobiology and genetics. The majority of determinants were however, included in the expert reviews of only one discipline within our study. Whilst a number of determinants are researched by two or more disciplines, multidisciplinary research into these determinants is rare. Early in our work we identified some relatively isolated multidisciplinary papers within the addiction field; work by West (2013) and Jacob et al. (2001) has drawn together evidence from across disciplines such as genetics and psychology to improve understanding of the determinants of addiction in relation to alcohol, nicotine and illicit drugs.

We discussed a number of individual determinants in the model where the respective disciplinary experts were unaware of any current or past multidisciplinary work suggesting a need for more multidisciplinary addiction research. However, it is evident in Figure 11 that, where a determinant shows input from multiple disciplines, the disciplines involved tend to focus on a similar level of analysis, (i.e. the cellular and molecular, individual or social environmental), and therefore may have more common research approaches and practices, which could facilitate multidisciplinary working in the future. Research working across epistemological backgrounds to understand addiction is rare in the literature to date.

Thus, to further our understanding of the determinants of addiction we should encourage researchers to work across disciplines and particularly across epistemologies in developing future addictions research. Policy makers and funding bodies should be aware that they might greatly further knowledge by supporting multidisciplinary research around the determinants of harmful substance use and gambling. Such multidisciplinarity and cross-epistemological research could enhance our understanding of substance use and gambling by drawing on learning from different disciplinary approaches in larger, co-ordinated multidisciplinary projects to aid in the design of effective intervention strategies to prevent harmful addictive substance use and harmful gambling.

Figure 11: alcohol model with multidisciplinary emphasis



3.4 Case Studies

To illustrate how the model depicted above can be used to further understanding of the determinants of the transition to harmful substance use or gambling, we have produced two illustrative case studies. These case studies relate to harmful alcohol consumption and are plausible but fictional scenarios[1]designed to show how different determinants work together within different individuals and dependent upon the social context of both the user and, more specifically, the use of the substance. They also illustrate that not all determinants need affect an individual engaging with a particular substance; some individuals might have four or five determinants of risky substance use whilst another has fourteen or fifteen. The case studies are not exhaustive but seek to highlight a range of potentially relevant determinants.

For each case study, we present the scenario in three different ways: firstly as a stand-alone brief text-based description, secondly as a brief text-based description with commentary, and finally within the model relating to the specific substance in question where relevant determinants are highlighted in black and the remaining determinants not relevant to the case study are shown in grey (Figures 12 and 13, p. 45 & 47).

Case study 1: Martin

Martin is a 58 year ex-procurement manager from an international manufacturing company. During his early working life, Martin was a moderate drinker. However, as his career progressed he gradually started to drink more and more alcohol; in part to manage his stressful work life and in part because his job required large amounts of international travel that included lavish nights out. In his mid- and late- 40s, Martin's alcohol consumption gradually rose to a minimum of a bottle of wine a night, often two. As a result of his drinking and the resultant unpredictable behaviour, his wife divorced him six years ago and he remains single today. Following the divorce he continued to drink heavily and problems at work combined with personal financial difficulties were important contributors to a nervous breakdown which led him to retire early at the age of 55. At this time he was forced to sell his house and move into council rented accommodation. During the first few months of retirement, Martin's drinking escalated to 2-3 bottles of whisky a week. After a year, Martin quit drinking because he felt unable to control his consumption and was concerned that it may be having a detrimental impact on his health. However, 12 months ago Martin began drinking once again and over the past year his consumption has gradually escalated. Martin most often drinks alone, at home. He has no family and has maintained few friendships since his illness. Recently,

[1] Some of the case studies draw minor elements from case studies in the published literature or research conducted by the authors.

following abnormal results from a liver function test, Martin was advised to quit drinking. Despite this, he continues to drink 1-2 bottles of wine a night because he finds that it helps him to relax.

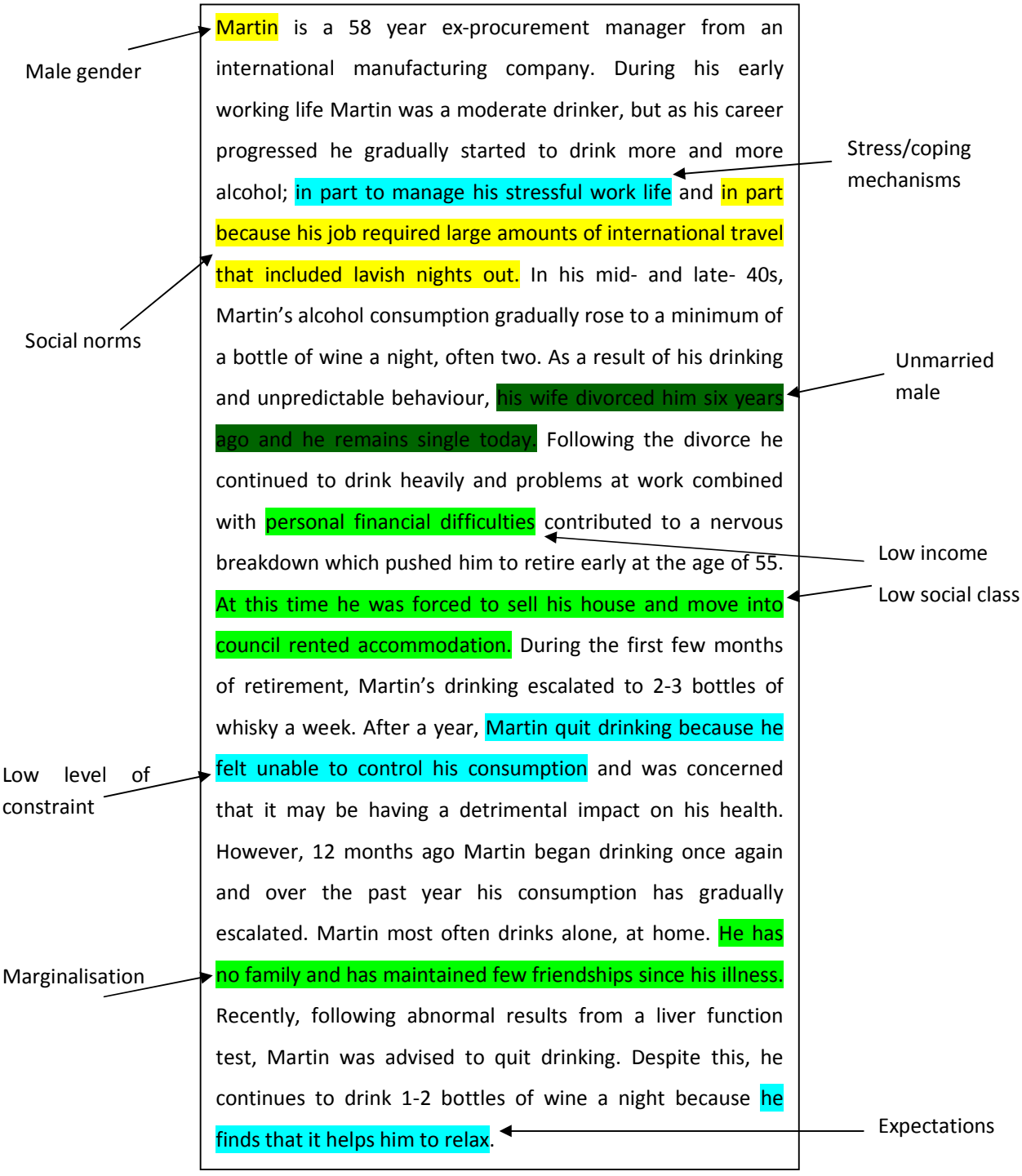
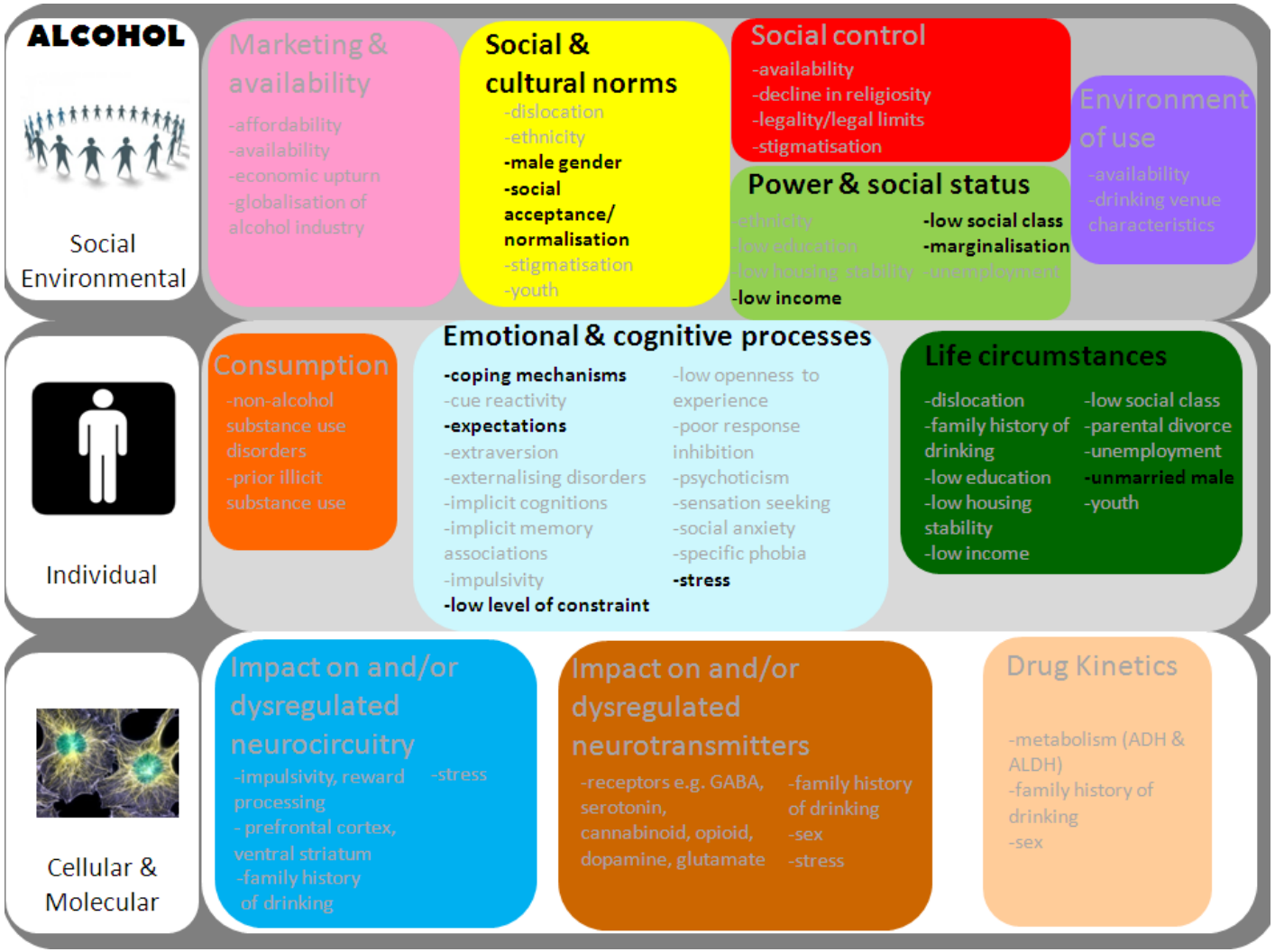


Figure 12: Case study 1 – Martin



Case study 2: Daniel

Daniel is a 23 year old trainee accountant living in London. He works hard during the week and enjoys letting off steam at the weekend with friends from work and his university days. They go out drinking every Friday and Saturday night, to bars and clubs around the city, usually staying out until 3 or 4am. Daniel has never smoked but he has been a binge drinker ever since he started university and, although no longer the case, he used to experiment with drugs with one group of university friends. All of Daniel's friends drink a similar amount when they are out, so they usually buy drinks in rounds. Their raucous nights out are usually uneventful, but last week they were in a really crowded pub and Daniel accidentally spilled his drink over someone around midnight. One thing led to another and the two men ended up fighting outside the pub. Daniel walked away with a broken cheek-bone.

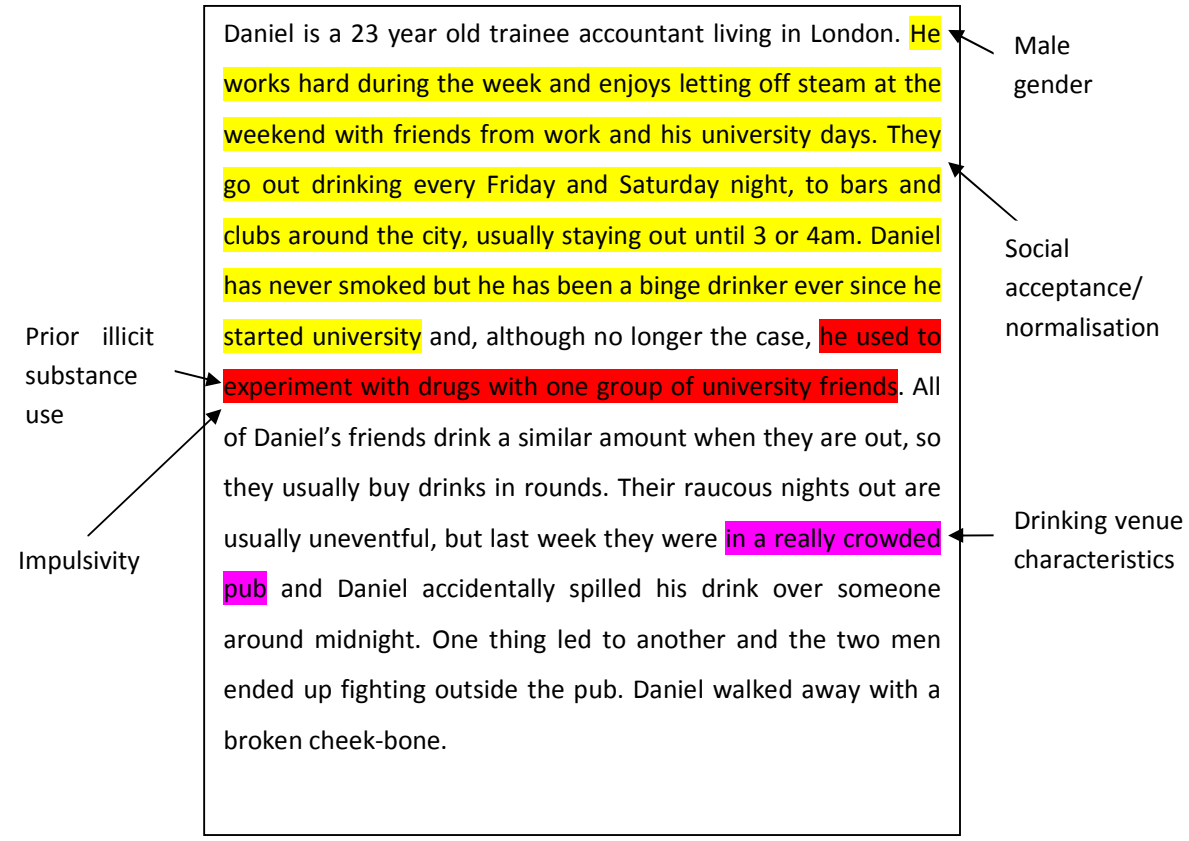
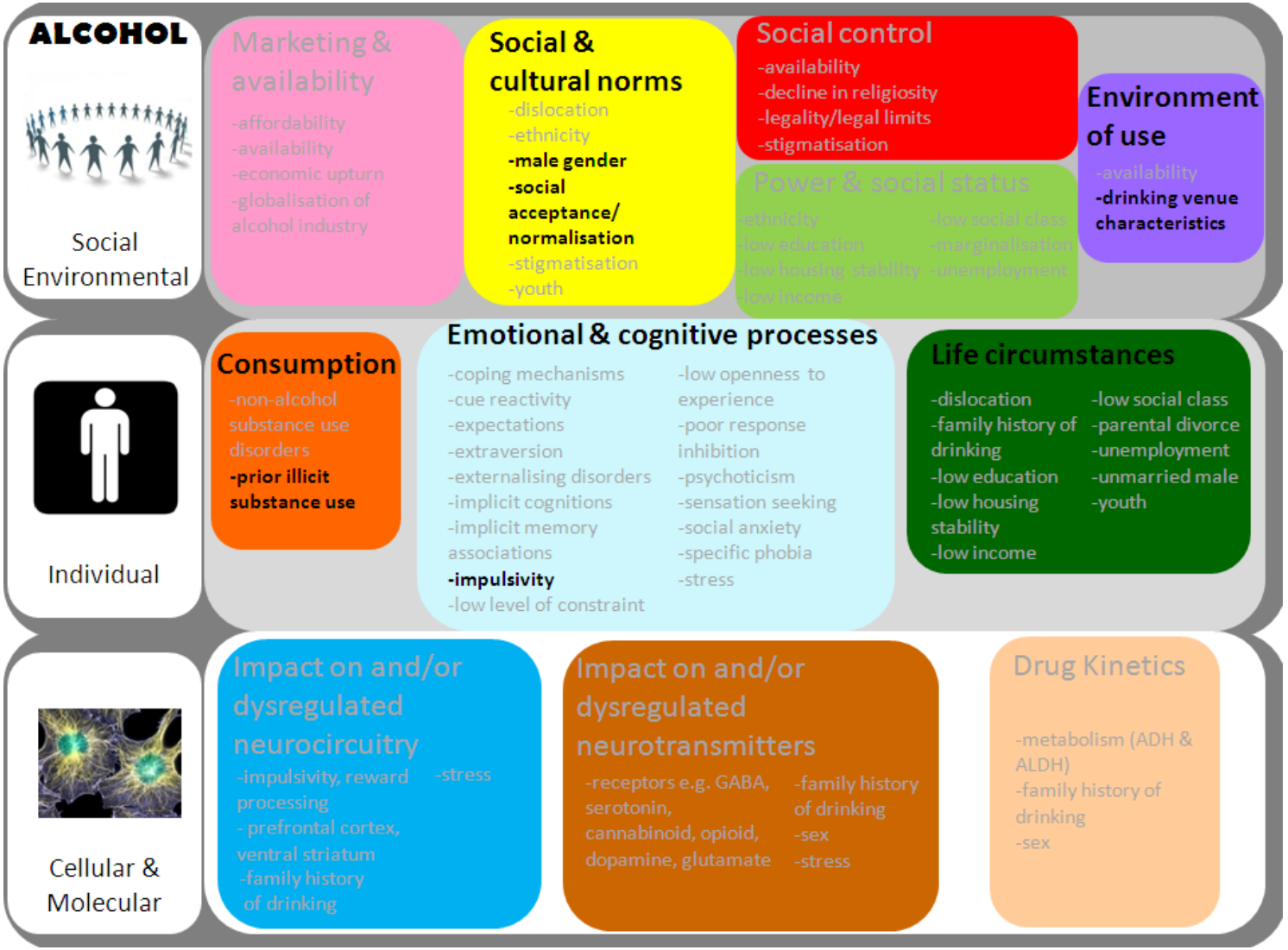


Figure 13: Case study 2 – Daniel



3.5 Transition probabilities

3.5.1 Sample description

From the first wave (baseline to T2) we included all 14 to 17 year olds (681 women and 714 men). Of participants, 63.6% reported lifetime comorbidity of any other mental disorder. From the second wave (T2 to T3) we included all 18 to 28 year olds (1383 women and 1408 men). In this subsample of participants 65.0 % reported lifetime comorbidity. The sample characteristics for transitions in nicotine use are displayed in Table 2. Frequencies of comorbidity presented here differ from the comorbidity of alcohol users presented in D7.2 report (McLeod et al. 2013) as alcohol abuse and dependence are included here as comorbidity. It is evident that the N changes substantially by operationalisation. The elevated figures for harmful use in Version B (in brackets) are a result of people smoking at least 20 cigarettes a day who are not diagnosed as nicotine dependent when being interviewed with the CIDI.

Table 2: Number of people included in calculations for transitions in nicotine consumption, stratified by age, gender, and comorbidity. Values derived from Version A (Version B). Version B are only displayed when different to Version A.

	Females				Males				Total	
	No comorbidity		Comorbidity		No comorbidity		Comorbidity			
Age group 14-17										
Total	238		443		301		413		1395	
Abstinent	209		327		275		307		1118	
User	12	(11)	54	(44)	15	(13)	53	(39)	134	(107)
Harmful user	17	(18)	62	(72)	11	(13)	53	(67)	143	(170)
Age group 18-22										
Total	162		438		215		408		1223	
Abstinent	124		221		146		189		680	
User	31	(24)	150	(110)	63	(36)	142	(84)	386	(254)
Harmful user	7	(14)	67	(107)	6	(33)	77	(135)	157	(289)
Age group 23-28										
Total	280		503		335		450		1568	
Abstinent	251		348		284		283		1166	
User	21	(16)	99	(65)	43	(25)	106	(49)	269	(155)
Harmful user	8	(13)	56	(90)	8	(26)	61	(118)	133	(247)

3.5.2 Transition probabilities

The crude transition probabilities (annual rates) for nicotine consumption (Versions A and B) are shown in Tables 3 and 4.

Table 3 Crude annual rates of transition for nicotine use in % for males and females with and without lifetime comorbidity. Results are based on Version A.

Age group	13 – 17			18 – 22			23 - 28		
Time 2 / Time 1	Abst.	User	Harm. user	Abst.	User	Harm. user	Abst.	User	Harm. user
Males without lifetime comorbidity									
Abstinent	-	4.8	0.5	-	1.9	0.0	-	1.8	0.0
User	14.7	-	2.3	7.1	-	0.0	6.3	-	0.0
Harmful user	8.2	15.0	-	0.0	0.0	-	0.0	0.0	-
Males with lifetime comorbidity									
Abstinent	-	7.2	2.7	-	3.0	0.0	-	1.9	0.0
User	4.5	-	7.5	6.8	-	0.0	8.5	-	0.0
Harmful user	4.1	13.2	-	0.0	0.0	-	0.0	0.0	-
Females without lifetime comorbidity									
Abstinent	-	4.0	0.6	-	1.5	0.0	-	1.7	0.0
User	15.4	-	2.1	7.9	-	0.0	9.4	-	0.0
Harmful user	15.0	5.9	-	0.0	0.0	-	0.0	0.0	-
Females with lifetime comorbidity									
Abstinent	-	6.2	2.4	-	2.4	0.0	-	1.5	0.0
User	3.7	-	6.1	8.2	-	0.0	8.4	-	0.0
Harmful user	8.8	11.0	-	0.0	0.0	-	0.0	0.0	-

Table 4 Crude annual rates of transition for nicotine use in % for males and females with and without lifetime comorbidity. Results are based on Version B.

Age group	13 - 17			18 – 22			23 - 28		
Time 2 / Time 1	Abst.	User	Harm. user	Abst.	User	Harm. user	Abst.	User	Harm. user
Males without lifetime comorbidity									
Abstinent	-	2.8	2.6	-	1.0	0.9	-	0.8	1.1
User	12.8	-	12.6	9.5	-	4.3	8.0	-	3.4
Harmful user	11.9	3.4	-	3.6	3.7	-	2.7	1.8	-
Males with lifetime comorbidity									
Abstinent	-	5.3	4.7	-	2.1	0.9	-	1.0	1.0
User	4.4	-	14.5	7.3	-	5.0	9.2	-	3.9
Harmful user	4.2	6.4	-	3.1	1.3	-	3.9	1.6	-
Females without lifetime comorbidity									
Abstinent	-	3.6	1.0	-	1.3	0.2	-	1.4	0.3
User	14.2	-	16.9	8.4	-	2.4	9.8	-	1.6
Harmful user	15.6	4.5	-	3.7	2.7	-	2.8	1.8	-
Females with lifetime comorbidity									
Abstinent	-	5.3	3.4	-	2.0	0.4	-	0.9	0.5
User	3.6	-	10.3	8.3	-	2.9	9.5	-	2.8
Harmful user	8.3	7.5	-	3.5	1.9	-	2.9	1.0	-

3.5.3 Simulations

Based on the transition probabilities shown in Tables 3 and 4, simulations were calculated for ages 13 to 30 on a fictitious sample of 100,000 persons. The simulations display the expected prevalence of each use category based on the age-, gender-, and comorbidity-specific transition probabilities.

Overall the results show rather stable rates of 10 to 20% harmful users with rather small gender differences. With respect to use as well as harmful use large differences between people with and without comorbidity can be observed with the latter showing substantially lower rates. It should be noted that the inclusion of the criterion of at least 20 cigarettes per day for harmful use leads to substantially higher rates of harmful use.

Figure 14: Simulations of nicotine consumption for males and females with and without lifetime comorbidity based on crude annual rates from Version A.

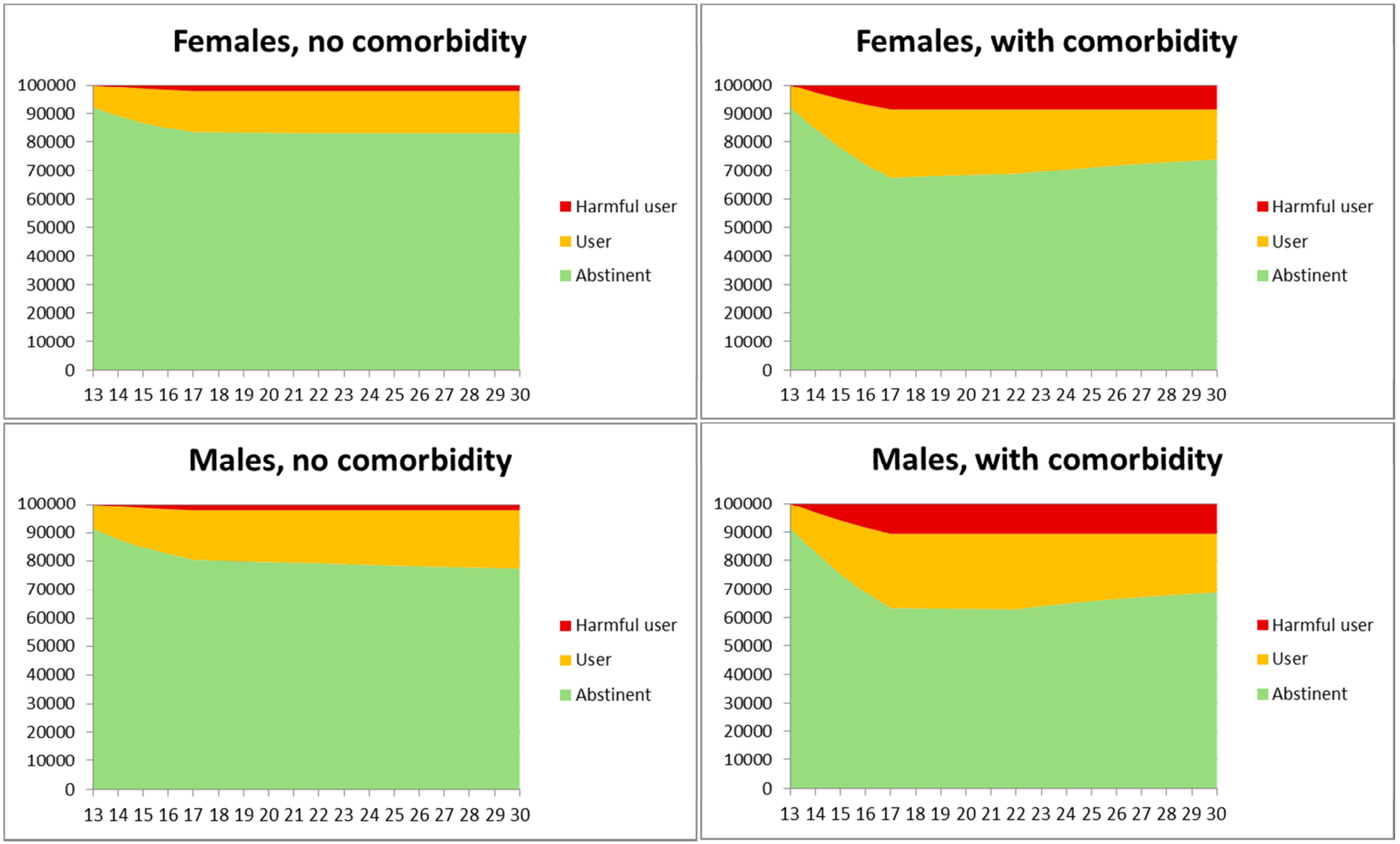
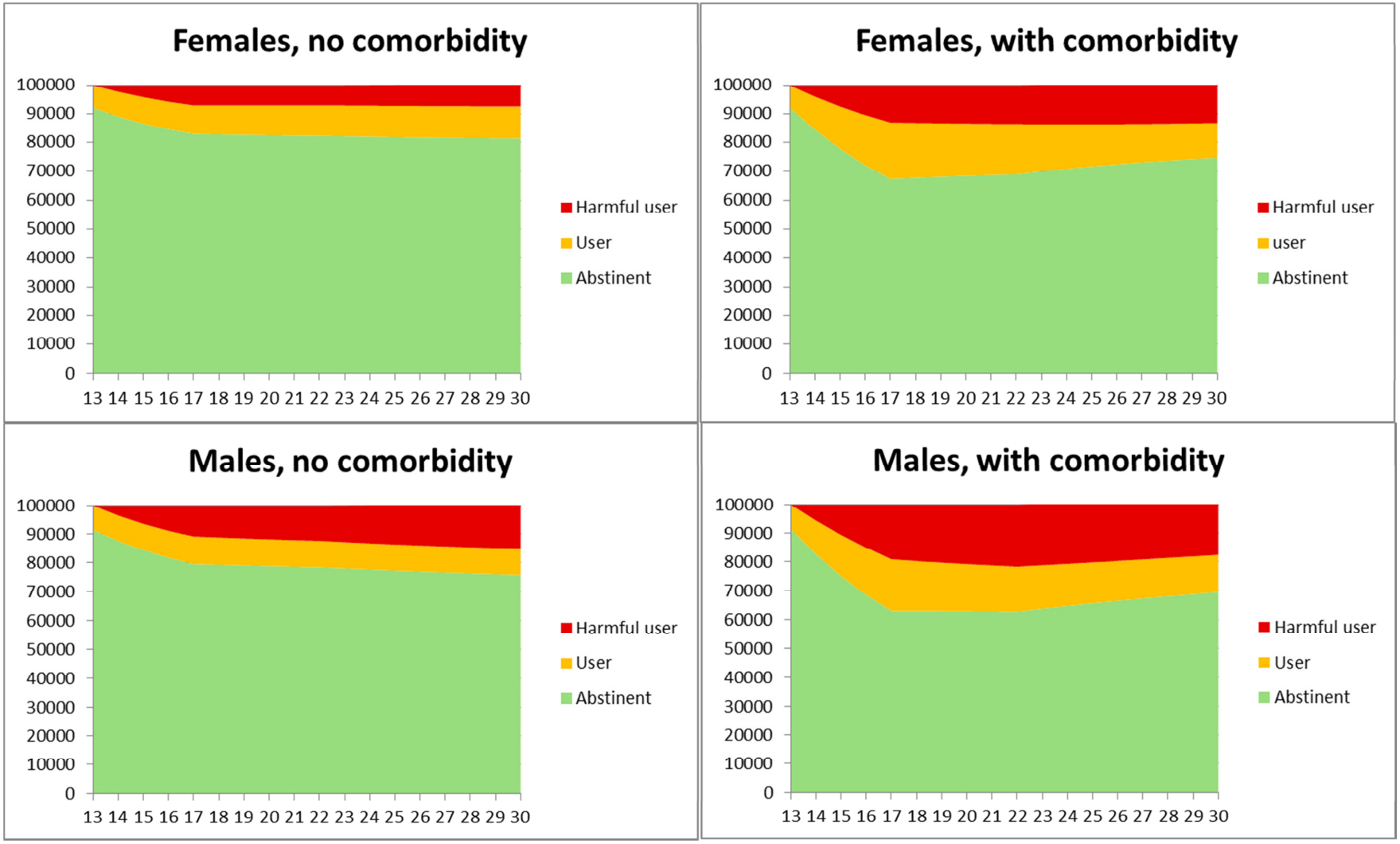


Figure 15: Simulations of nicotine consumption for males and females with and without lifetime comorbidity based on crude annual rates from Version B.



4. DISCUSSION

4.1 Models

4.1.1 Key findings

The models presented here for addictive substances and gambling demonstrate a multidisciplinary understanding of the key determinants of the transition from risky use to harmful substance use and harmful gambling. We have grouped these determinants into key themes, which provide easy ways to understand the mechanisms by which these determinants may function and consequently infer possible policy responses and interventions.

The models for the legal addictive behaviours of alcohol, tobacco and gambling, and that for cannabis, which is not as heavily regulated or stigmatised, show that personal factors, exemplified at both the individual and cellular and molecular levels of analysis, total the greatest number of determinants of harmful use. These far outweigh the number of behavioural determinants which are contributed at the socio-environmental level. This is in contrast to our previous report, which focused upon risky use, and highlighted the important role the environment has to play in determining an individual's risky use of substances and gambling (McLeod et al. 2013). The current report emphasises the importance of the internalisation of affective processes which take place during the increasing harmful use of substances and gambling. It also stresses the need to focus policy and research addressing harmful use toward individual level and innate mechanisms (Selin, 2005).

The models for the illegal substances of stimulants, opioids and club drugs contrast to others presented here in terms of the limited number of determinants that we have identified for the harmful use of these substances. In part, this highlights the lack of available evidence surrounding these substances, which possibly stems from their illegal nature, making them more difficult to study. This dearth highlights the need for an increased research focus within this area if we want to better understand the determinants of the development of the harmful use of such substances. Within the stimulants, opioids and club drugs models particularly few determinants lie at the individual level of analysis; on reflection this may be a result of the tendency for disciplines focused at the individual level, such as psychology, to focus their research around legal and more widespread behaviours such as alcohol and gambling.

We have included for consideration a version of the model which displays those determinants common to the harmful use of all the substances examined here and gambling. This model reveals that very few determinants are common to all the harmful behaviours, with all but two common determinants lying at the biological level. This version of the model highlights the fractured nature of the addiction research field in

that use of many of the substances are studied separately by different research groups and different terminology and theories used by each of the groups may prevent unification of a total hypothesis of harmful use across all the substances and gambling. However, the relatively few determinants in this model may be a result of the way that we have chosen to break down the models into different substances and gambling, separating out the determinants of use of illicit substances into individual models which, perhaps as a result of a lack of research, are themselves sparsely populated. If we were to cluster determinants operating across multiple legal versus illegal behaviours, or to exclude the behavioural addiction of gambling, then this model displaying common determinants would look very different.

Within the gambling model there exists a theme domain 'Structural and situational characteristics of gambling activities', which is outside of the three focus levels of our model. This theme displays determinants related to game characteristics which increase harmful use. We decided to place this outside the three-layered model as did not fit within the original structure. Within the other models, a comparable theme of drug characteristics is not relevant as each of the substances is outlined within its own model. The equivalent would have been to separate out different gambling activities such as slot machines versus roulette versus racing bets. However, that was beyond the scope of this work.

We have also presented a model highlighting determinants that are studied within multiple disciplines (Figure 11, alcohol). This model identifies patterns within existing research, such as the increased overlap of research surrounding determinants at the cellular and molecular level in comparison to the other levels of focus. In presenting the determinants by the discipline from which they originate, we are able to identify focus points for potential future multidisciplinary research. Such multidisciplinary research will be essential to further our understanding of the development of addictive behaviours.

4.1.2 Limitations

Our research carries a number of limitations resulting from both the evidence available to use from previous research publications and our study design.

Within our definition of harmful use of substances and gambling we have included both harms resulting from use to the user, such as health harms and financial difficulties resulting from substance use and also harms pertaining to others, such as a user's family which may suffer from their use or members of society who may feel unsafe within their community due to drug-associated crimes. With such a broad category of harm, it is difficult to accurately display the type of harm resulting from such behaviours within our model format, with different studies using alternative definitions of harms, from dependence to violence to

psychological harms, and so some of the detail is lost to the user. Moreover, the concept of harms to others is not as well researched within the literature, and further research is required to further our understanding of the determinants of such behaviour.

Many of the limitations which arose during the preparation of the models surrounding risky use (McLeod et al. 2013) are also applicable to our work here concerning models of harmful substance use and harmful gambling, as the delineation between the two concepts is not clear within the available published literature, and so much of the literature has been used to support the work of both addictive stages. Research thinking and the literature do not, for the most part, align with the transitions that we have studied in this project. Whilst we commonly find studies that predict or find correlates for the onset of harmful use or addiction, it is much rarer to find studies which examine who among those using in a risky way move on to experiencing harm. The lack of such research means that we have a limited knowledge of who under what circumstances, among the considerably larger population using or behaving hazardously, comes to harm.

Additionally, the limitations arising from difficulties in assembling the data from disciplines with different ontologies and research practices which became apparent during our work surrounding risky substance use and risky gambling remain within this work.

It must be acknowledged that this range of models is specific to the range of disciplines that have contributed to work area 3 of ALICE RAP and the time frame within which it has been generated. If this model had been informed by a different panel of experts in different disciplines, for example biochemistry, law or history, the model would contain some different determinants. Further, our expert panel from across all the disciplines was bias towards alcohol research. Consequently, our model of the determinants of alcohol use shows a greater number of determinants than that of tobacco, gambling or the illicit substances. If the research focus of our expert panel was weighted differently then the models presented here would display a different level of understanding of the different harmful behaviours examined. Similarly, if this model were to be generated in a decade's time again the determinants considered important would be different than those highlighted here; as addiction studies move forward key theories and determinants will change in light of new evidence. However, it is important to not only assess the current position of knowledge within the field, of which these models provide an overview for factors contributing to harmful substance use or gambling, but also to provide workable models for future research to build upon. Our models highlight current knowledge gaps specific to different addictive behaviours, whilst presenting key determinants around which different discipline experts can collaborate to enhance our understanding.

During our research, we repeatedly came across the problem of lack of definition within the literature regarding the substances studied. Many reports cite illicit substances as one category, without stating which of these substances their work pertains to (Swendsen et al. 2010) and in such cases we felt it impossible to include such datasets within our own work.

Finally, all the studies cited across the disciplines in our review of the evidence on determinants of harmful substance use and harmful gambling reported at least one significant effect of a determinant on harmful use. This suggests a publication bias is in operation, whereby journals publish significant results and reject null findings. The magnitude of this 'file drawer' effect are impossible to determine, and thus the determinants listed within the models presented here must be interpreted with caution.

4.2 Transition Probabilities

The prevalence modelled for nicotine use (use and harmful use together) range between 20 and 30% among people aged at least 18. Given the substantial health risks that are associated even with the consumption of one to four cigarettes per day (Bjartveit & Tverdal 2005), these prevalence display an important threat to public health. The recent European Tobacco Control Status Report stated that Europe trails behind (all) other countries with respect to bans of smoking in public places and tobacco advertising, promotion and sponsorship bans (World Health Organisation 2013a).

The transition probabilities for switching from harmful use back to use or abstinence are very low for the ages 18 to 28. This is in line with common knowledge about the relative persistence of nicotine dependence. At lower ages the transition probabilities indicate higher flexibility to switch categories of use. Preventive measures should consequently try to reach smokers at young ages.

4.2.1 Methodological limitations

We did not have enough cases to reliably calculate all single transitions (for details see full report on transition probabilities). So far errors in measurement and uncertainty, i.e. confidence intervals, were not taken into account. Especially in the younger age group this might have let to inconsistent transition probabilities. Nevertheless, the results are quite stable across variants of operationalisation, indicating a relative robustness of our results.

Due to the design of the main underlying study, which had measurement points only after several years, we had to calculate transition probabilities in age groups instead of calculating transitions for each year of age

separately. Therefore one has to keep in mind that the peak at age 17 may be impacted by the specific age categories we selected (based on the legal drinking age). Different cut-offs for age groupings might have led to a slightly different shape.

Unfortunately we had to calculate transition probabilities on overlapping populations, so the estimations are not independent. Transition probabilities for the youngest age group rely on the same persons as those for the middle and the oldest age group. Transitions for the middle the oldest age group are based on an exhaustive set of persons. Also, we do not have any information from the main study on how transition probabilities change with increasing age above 30. Therefore we need another cross sectional, representative study investigating an older cohort.

In terms of the operationalisation of substance use in general and nicotine use specifically it would be desirable to develop universally used thresholds for (risky and) harmful use such as used by the European Medicines Agency (Rehm et al. 2006b) based on earlier work from the World Health Organization (World Health Organisation 2001), see also the proposal of Rehm and Roerecke (2013). Concerning the inclusion of mean daily consumption we may have to break down a continuum into distinct categories which will always be to a certain extend arbitrary. Nevertheless it would increase comparability of research results. For nicotine we need a debate on the question if there even is a distinct category of consumption behaviour that we would explicitly label as risky. Or to put it another way if in the case of nicotine any use should be described as risky since already small daily doses bear high risks (Bjartveit & Tverdal, 2005). Unlike the J-shaped curve we observe for alcohol consumption and diseases (Corrao et al. 2004) or total mortality (Di et al. 2006), a steady increase of risk severe disease as lung cancer (Law et al. 1997) or bronchial carcinoma (Doll & Peto 1978) is observed from the first cigarette.

4.2.2 Generalisability

How do these results from a Bavarian, German sample apply to other regions within Europe and across the world? It should be noted, that a number of restrictive policy measures (tax increases, smoke-free workplace regulations, warning notices) were established in Germany in the years since 2002 which has led to a decreasing prevalence of adolescent smokers in recent years (Schaller & P+Âtschke-Langer 2012). The prevalence estimated in the modelling however match the estimated prevalence of adult smokers in Germany of about 25 % (World Health Organisation 2013b). Even though European countries differ in the extent of tobacco control measures (World Health Organisation 2013a), adult smoking prevalence are comparable, ranging mostly between 20 and 30%.

This implies that we need two things: first of all we need separate country- or region-specific calculations of transition probabilities and second we need to investigate in detail those factors that make the difference. In this manner we may be able to derive useful public health measures to decrease the probability of an individual transitioning into harmful or risky patterns and support transitions into less risky patterns of use or abstinence.

4.3 Consequences for EU research and health policy

As already stated in our model report for the determinants of risky substance use and risky gambling (McLeod et al, 2013) one of the novel features of our work is the separation of the analyses of determinants of the aetiopathological pathways of risky use and harmful use. This separation has major advantages for the formulation of research questions in order to better understand these long-term processes, for clinical practice as well as for health and broader social policy. It is important to note that at this point, hardly any of the available research literature is based upon this separation of the aetiopathological pathway of substance use and gambling. One implication of this lack of knowledge is, that the determination of early factors of the transition into risky use is very difficult using the presently available literature. Those determinants, were they available, would help us to study the type and impact of early interventions required to avoid long-term negative consequences (McLeod et al, 2013). Equally, for this report on the determinants of harmful substance use and harmful gambling, a highly relevant conclusion is the need for further research on very specific determinants for the transition from risky use to harmful use. In addition to this basic conclusion we have formulated several consequences from our work for research, clinical practice and policy.

4.3.1 Consequences for EU Research

(1) To focus research on the transition processes and relevant factors leading from risky to harmful use.
There is some evidence that individual vulnerability – compared to environmental factors – plays the major role in this stage of development. However, a clear understanding of the exact factors and processes which lead some individuals to make the transition from risky use to harmful use, whilst others remain as risky substance users and risky gamblers or even reduce their usage to that of an unproblematic pattern still elude us.

(2) To focus research on the subjective experiences of the individuals during the transition from risky to harmful use and gambling.

E.g., we do not know if and when individuals realize that their behaviour is becoming problematic, what the critical indicators of this may be, if the individuals know what to do in order to deal with such a problem, and what factors may be supportive in helping to change ones behaviour without external support.

(3) To focus research on the observation of early developments of harmful use by professionals and significant others.

We have very limited knowledge if societal members, for example family members, supervisors at work or teachers in the school can effectively recognize early developments in the progression to harmful substance use or harmful gambling, and if they know how to react, and what the possible effects are. A better understanding of these very first signals and processes would help us to provide adequate early support to individuals by significant others within their environment.

(4) To study commonalities and differences between harmful substance use and harmful gambling.

There is increasing scientific knowledge in this field that is revealing a pattern of commonalities and differences for the transition from risky to harmful substance use and gambling, which is at present not well understood. In spite of the big differences underlying the consumption of psychotropic substances in a case of harmful use, there are many common factors on both the environmental and individual level, including new biological correlates. But a better understanding of these developments is necessary to be able to target specific early interventions during these processes.

(5) To promote research on different aspects of harmful use and gambling beyond clinically diagnosed and relevant substance use and gambling disorders.

Currently research is focused on the negative impact of substance use disorders, especially addiction. There is not enough knowledge on the early forms of harm, e.g. in a social field (family interactions, work performance, early negative physiological developments). A better understanding in these fields would help to promote prevention and early intervention activities.

(6) To better understand the relevant factors and processes of socio-economic, cultural and environmental conditions and their impact upon harmful use.

There is evidence that different environmental factors like marginalization, marketing, living and working conditions and the legal situation concerning licit and illicit drugs has an impact on the size of the problem of harmful use in a given country. Prevalence rates between countries of similar cultures differ vastly so that there is no doubt about the influence of such factors. However, until now we have

lacked an understanding of how these determinants impact the development of harmful use and what the relevance of the different groups of determinants is. Relevant questions are among others: Do these groups of determinants only have an impact for subjects with a higher individual vulnerability, or when analyzing large population groups? Do environmental factors play a role for subjects with a low level of vulnerability? Do different types of factors have a different impact, and further differ in their impact on different sub-groups? A better scientific understanding is a precondition for a targeted modification of environmental determinants.

(7) To better understand the impact of determinants from the field of cellular and molecular factors.

There is increasing knowledge that genetic variations and certain adaptive processes increase the risk for harmful use. It is not yet clear whether the extent of a risk increase for certain individuals or sub-groups is relevant for public health action, or if the possible impact of determinants on this level is initiated by environmental factors and behavioural conditions and competences. Public health impact would mean that the risk increase of such a determinant for harmful use is significant enough to develop models of early detection and early intervention. This topic also covers basic ethical considerations.

4.3.2 Consequences for clinical practice

Harmful use and harmful gambling is the classical focus of any form of professional treatment. From our research we suggest the following consequences for clinical practice:

(8) To make the support more attractive and develop more effective forms of early interventions.

Traditionally society and the individual environment waits too long until a person is either motivated or forced (for health and social reasons) to go into treatment. Late treatment is costly and the relapse risk is high. Therefore, any approaches which offer earlier interventions are recommended.

(9) To offer more (early) therapeutic interventions in the general health and social care system.

The traditional specialized treatment system for addicted subjects is helpful for people with a severe development. But people in an earlier stage, especially with very low early forms of harm, do not want to be stigmatized by an alcohol or drug treatment centre. They would prefer more neutral treatment possibilities. This might be – depending on the national health and social care system – a general practitioner, general psycho-social and psychiatric counselling and treatment centre, outpatient offices of psychotherapists and similar agencies.

4.3.3 Consequences for health and broader social policy

(10) To reduce social determinants for harmful use.

Marginalization, marketing, negative living and working conditions are examples for social determinants of harmful use. A preventive public health policy should try to reduce the risk and impact of these determinants on individual behaviour.

(11) To integrate as much as possible the currently predominant specialized addiction treatment and care system into the general health and social care.

Specialized addiction care and treatment facilities reduced the acceptance of seeking early treatment for subjects who do not yet feel addicted and increase the marginalization by handling them as a separate “high-risk group”. All efforts should be made, to provide where possible early counselling and treatment in facilities of the general health and social system. This includes among others general practitioners, general hospitals, social services, psychotherapeutic practices.

5. CONCLUSIONS

The major conclusions arising from this work are:

- The determinants underlying the transition from risky use to harmful use of substances or gambling are complex in nature and span factors from the molecular and cellular through the individual to the environment.
- The influence of an individual's vulnerability and personal factors in the development of harmful substance use and harmful gambling among those already behaving riskily is greater than and more acutely understood than the influence of environmental factors, at least for behaviours which have been well researched and documented within the literature.
- The harms which derive from substance use and gambling extend well beyond those attributed to the dependent user, and include individuals with problematic usage patterns and harms to others.
- An increased research focus on the different aspects of harmful use is required to increase understanding and produce effective strategies for the prevention of harm to individuals and society.
- In order to address problems of harmful substance use and gambling society as a whole must work to overcome key issues, for example social and cultural norms, through tackling factors such as the acceptance and image of substance use and gambling, and the marketing and other commercial promotion.
- Increased levels of multidisciplinary research within this field are necessary to fill knowledge gaps and highlight possible effective future strategies in dealing with problems of harmful use.
- Clarification of multi-dimensional concepts, such as impulsivity, and usage patterns and their classification as heavy-, harmful- etc., within published research is essential to allow the unification of future research findings.

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APPENDIX 1: Glossary of determinants

This glossary includes all the determinants that occur within the model for each different substance and gambling. A number of determinants (listed first below) are not defined because they were deemed self-explanatory:

- Decline in religiosity
- Divorced/ Separated marital status
- Early age at alcohol use onset
- Early age at nicotine use onset
- Early age of onset of cannabis use
- Family history of drinking
- Family history of smoking
- Gambling promotions
- Globalisation of alcohol industry
- High jackpot size
- Low education
- Low income
- Male gender
- Parent/sibling use
- Parental divorce
- Personal alcohol use
- Prior illicit substance use
- Sex
- Stress
- Unemployment
- Unmarried male
- Youth

Accessibility – the extent to which people are able to find an individual or business selling a product, with high accessibility referring to a state in which a product is easy to find.

AChRs – an acetylcholine receptor is an integral membrane protein that responds to the binding of acetylcholine, a neurotransmitter. Acetylcholine receptors are classified according to their sensitivity to different molecules, for example nicotine.

Affordability – the state of being cheap enough for people to be able to buy, with high affordability referring to a price at which many people can afford to buy a product.

Agoraphobia – a fear of being in situations where escape might be difficult, or help wouldn't be available if things go wrong, for example when travelling on public transport or leaving home .

Anxiety disorders – an unpleasant state of inner turmoil, often accompanied by nervous behaviour (e.g. pacing). It is a subjectively unpleasant feeling of dread over something unlikely to happen.

Availability – the extent to which something is easily obtainable and ready for use. Availability and accessibility are often used interchangeably.

Baseline alterations in neurocircuitry – endogenous differences in brain receptors, transporters and neurotransmitters that may confer increased or decreased susceptibility to harmful substance use or gambling.

Bipolar disorder– a condition that effects one's mood, where it can swing from one extreme to the other. Often characterised by episodes of mania and depression.

Branding –the process involved in creating a unique name and image for a product in the consumers' mind. Branding aims to establish a significant and differentiated presence in the market that attracts and retains loyal customers (such as mild or menthol cigarettes).

Cognitive distortions – exaggerated or irrational thoughts that are believed to perpetuate the effects of certain states such as anxiety and depression.

Coping mechanism – the coping skills or strategies that people use to manage difficult situations.

Criminalisation – the process by which behaviours are transformed into crimes and individuals become criminals.

Cue reactivity – physiological and subjective reactions to presentations of drug-related stimuli (e.g. cigarettes or alcohol bottles) or being in an environment associated with drug use.

Depression – a medical illness that causes a constant feeling of sadness and lack of interest, affecting how a person feels, behaves and thinks.

Descriptive norms – perceptions regarding typical behaviour in given situations, usually based on observations and perceptions of the behaviour of those around you.

Dislocation– a break-down in the psychological integration of individuals within a community, for example as a result of a natural disaster, accident, conflict or violence and economic change (Alexander, 2008). Individuals and groups in society become dislocated or alienated to a greater or lesser extent, with severely dislocated individuals potentially struggling to find psychosocial integration and therefore constructing a lifestyle that substitutes it.

Drinking venue characteristics – for example, designing pub/bar/club layout to minimise violence or encourage drinking.

Drug driving– driving under the influence of illicit substances.

Early positive reactions to use – positive experiences of use early in the use career.

Economic downturn – a general slowdown in economic activity.

Economic upturn –a general upturn in economic activity.

Ethnicity –a socially defined category of people who identify with each other based on a shared social experience or ancestry.

Expectancies – the state of thinking or hoping that something, especially something good, will happen as a result of performing a given behaviour.

Externalising disorders – problem behaviours are directed outwards towards other people, for example through disobedience, aggression and delinquency.

Extraversion – extraversion is manifested in outgoing, talkative, energetic behaviour.

High event frequency – high number of opportunities to gamble within a given time period.

Implicit cognitions– unconscious influences (such as memory or perception) that influence an individual's behaviour.

Implicit memory associations –unconscious recall of memories associated with a behaviour.

Impulsivity – a multi-factorial construct that involves a tendency to act on a whim, displaying behaviour characterized by little or no forethought, reflection, or consideration of the consequences.

Lack of access to drug services – including both the availability of drug services (such as substitute prescribing or residential rehabilitation) in a society and individual difficulties in accessing services those services (e.g. due to geographical location or funding restrictions).

Lack of secure environment for use – absence of environments that reduce harm to illicit substance users, such as needle exchange facilities and supervised injection sites.

Legal limits/legality – the legal status of a substance or behaviour within a society, including the age at which consumption of a particular substance becomes legal. For example, in certain countries alcohol is prohibited whilst in others it is legal to drink above a certain age (e.g. 18 or 21 years).

Light, color, and sound effects – of gambling machinery.

Low consciousness – a low level of awareness of internal or external stimuli.

Low housing stability – an inability to retain housing, for example due to lack of affordability.

Low level of constraint– inability to say no or stop engagement with a behaviour once started.

Low social class –social class describes people with the same social, economic, or educational status. Low social class therefore describes people with low social, economic or educational status.

Marginalisation – the social process of becoming or being made marginal that can apply to an individual or group within a larger society.

Metabolism– chemical transformations that sustain life within the cells of living organsims.

Mood disorders –a psychological disorder characterized by the elevation or lowering of a person's mood, such as depression or bipolar disorder.

Novelty seeking – a personality trait associated with impulsive decision making, extravagance in approach to reward cue and curiosity and exploratory activity in the face of novel stimuli.

Openness to experience – a global personality trait of habits and tendencies (such as active imagination, attentiveness to inner feelings, preference for variety and curiosity) that may cluster together.

Poor response inhibition – the inability to of an individual to keeps in mind goals and prioritise actions, giving rise to poor impulse control.

Prefrontal cortex – the anterior part of the frontal lobes of the brain. Lying in front of the motor and pre-motor areas, this part of the brain effects our expression of personality, decision making and social behaviours.

Price promotions – offers on a purchase price making products more affordable, for example 'buy one get one free' and '25% off if you buy 6 bottle' deals.

Psychoticism – a personality pattern characterised by aggression and interpersonal hostility.

Receptors –differentreceptor genes may confer susceptibility to the risky use of substances or gambling (e.g. dopamine, nicotinic, serotonin, opioid, etc.)

Reward processing – the systems within the brain, involved with learning, responsible for positive or negative feedback following certain actions.

Route of consumption/delivery – the method use to ingest a substance (e.g. smoking, snorting or injection).

Sensation seeking – a personality trait defined by the search for experiences and feelings, that are "varied, novel, complex and intense", and by the readiness to "take physical, social, legal, and financial risks for the sake of such experiences."

Short pay out intervals – short time frame between opportunities to win when gambling.

Social acceptance/normalisation – the acceptability of a behaviour within a given culture or society at a given point in time.

Social anxiety–a persistent fear about social situations and being around people.

Specific phobia– a term used to describe any kind of anxiety disorder that is characterised by an unreasonable or irrational fear of specific objects or situations.

Stigmatisation – the process of identifying or highlighting something as bad.

Substance use disorders– the overuse of or dependence on a drug (such as alcohol or an illicit substance) that has detrimental effects on the individual's physical and mental health, or that of other people around them.

Ventral striatum – a part of the brain that facilitates and balances motivation with both higher- and lower-level functions, such as inhibiting behaviour in complex social interactions.

Visible near miss features – A near miss is a failure to reach a goal that comes close to being successful. A near miss may be taken as encouragement that a game strategy is working, raising hopes for future success, even in games of pure chance such as slots or lotteries where strategy does not impact on outcome. Some gambling systems are contrived to present a higher number of near misses than would be seen by chance alone.

APPENDIX 2: Evidence base for the determinants included in the models

Alcohol

Determinant	References
Affordability	(Booth et al. 2008; Carpenter & Dobkin 2010; Cawley & Ruhm 2011; Chaloupka et al. 2002; Cook & Moore 1993; Elder et al. 2010; Farrell et al. 2003; Foster & Ferguson 2012; Gallet 2007; Grube & Stewart 2004; Wagenaar 2010; Wagenaar et al. 2009)
Availability	(Rowland et al. 2014; Stockwell et al. 2013)
Coping mechanisms	(Greenfield et al. 2009; Hasking et al. 2011; Holahan et al. 2001)
Cue reactivity	(Bjork et al. 2012; Wrase et al. 2002)
Decline in religiosity	(Conrad 1992; Conrad & Schneider 1980)
Dislocation	(Alexander 2010)
Drink driving	(Ramaekers et al. 2000)
Drinking venue characteristics	(Hughes et al. 2011; Stead et al. 2012)
Economic upturn	(Ettner 1997; Pacula 2011; Ruhm & Black 2002)
Ethnicity	(Peralta et al. 2010)
Expectations	(Greenfield et al. 2009; Hasking et al. 2011)
Externalising disorders	(Behrendt et al. 2011; Knop et al. 2009; Lee et al. 2011; Tuithof et al. 2012)
Extraversion	(Grekin et al. 2006)
Family history of drinking	(Agrawal & Lynskey 2008; Bierut et al. 2004; Cadoret et al. 1996; Cadoret et al. 1995; Cloninger et al. 1985)
Globalisation of alcohol industry	(Colson & Scudder 1988)
Implicit cognitions	(Stacy & Wiers 2010; Wiers et al. 2013)
Implicit memory associations	(Rooke et al. 2008)
Impulsivity	(Bjork et al. 2012; Blonigen et al. 2011; Garavan & Weierstall 2012; Verdejo-Garcia et al. 2008; von et al. 2008)
Legality/Legal limits	(Purssell et al. 2009; Room et al. 2006)
Low education	(Makela 1999; Storbjork & Room 2008)
Low housing stability	(Makela 1999; Storbjork & Room 2008)
Low income	(Makela 1999)
Low level of constraint	(Elkins et al. 2006)
Low openness to experience	(Grekin et al. 2006)
Low social class	(Makela & Paljarvi 2008; Makela 1999; Room 2001; Room 2005)
Male gender	(Makela et al. 2011; Room et al. 2011; Room & Hradilova Selin 2004; Storbjork & Room 2008)
Marginalisation	(Makela & Paljarvi 2008; Makela 1999; Room 2001; Room 2005)
Metabolism	(Kim 2009; Li et al. 2003; Prescott & Kendler 1999; Reich et al.

Determinant		References
		1998)
Non-alcohol substance use disorders		(Behrendt et al. 2011)
Poor response inhibition		(Nigg et al. 2006)
Prefrontal cortex		(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)
Prior illicit substance use		(Swendsen et al. 2010)
Psychoticism		(Sher et al. 2000)
Receptors	Dopamine	(Blum et al. 2011; Blum et al. 2010; Comings et al. 1999; Crabbe 2002; Volkow et al. 2004; Volkow et al. 2006; Volkow et al. 2007)
	GABA	(Agrawal et al. 2012; Cui et al. 2012; Li & Burmeister 2009; Nie et al. 2011; Rewal et al. 2012)
	Glutamate	(Breese et al. 2005; Cippitelli et al. 2010; Duka et al. 2003; Fadda & Rossetti 1998; Gass et al. 2011; Hayes et al. 2013; Heilig et al. 2010; Tsai & Coyle 1998; Xi & Stein 2002)
	Opioid	(Bart et al. 2004; Bart et al. 2005; Glatt et al. 2007; Hall et al. 2001; Koob 2006; Williams et al. 2007)
	Serotonin	(Bowers 2000; Crabbe 2002; Heinz et al. ; McHugh et al. 2010)
Reward processing		(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)
Sensation seeking		(Kim & Kim 2012; van et al. 2005)
Sex		(Kim 2009; Li et al. 2003; Prescott & Kendler 1999; Reich et al. 1998)
Social acceptance/ normalisation		(Gmel et al. 2010; Hallgren et al. 2012; Livingston et al. 2010; Partanen 1991; Room 2007; Room & Makela 2000; Rootman & Moser 1984; Skog 1985; Weisner & Schmidt 1995)
Social anxiety		(Buckner et al. 2008)
Specific phobia		(Swendsen et al. 2010)
Stigmatisation		(Room 2001; Room 2005; Skog 1985)
Stress		(Kiefer & Wiedemann 2004; Koob & Volkow 2010b; Rosenberg & Mazzola 2007; Sinha 2007; Sinha & Li 2007; Wand & Dobs 1991)
Unemployment		(Davalos et al. 2012; Eliason & Storrie 2009; Garcy & Vagero 2012; Henkel 2011; Tomkins et al. 2007)
Ventral striatum		(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)
Youth		(Room & Hradilova Selin 2004)

Tobacco

Determinants		References
Affordability		(Chaloupka et al. 2002; Chaloupka et al. 2011; Gallet & List 2003; Grossman 2005)
Agoraphobia		(Swendsen et al. 2010)
Bipolar disorder		(Swendsen et al. 2010)
Branding		(Capella et al. 2011; Hastings et al. 2008; National Cancer Institute 2008; Paynter & Edwards 2009)
Cue reactivity		(Engelmann et al. 2012)
Depression		(Swendsen et al. 2010)
Economic upturn		(Cawley & Ruhm 2011; Xu & Kaestner 2010)
Enclosed spaces		(England Department of Health 2011)
Externalising disorders		(Lee et al. 2011)
Family history of smoking		(Agrawal & Lynskey 2008; Agrawal et al. 2012; Huizink et al. 2010; Li et al. 2003)
High openness to experience		(Grekin et al. 2006)
Legality/legal limits		(Nutt 2012)
Low consciousness		(Grekin et al. 2006)
Low level of constraint		(Elkins et al. 2006)
Metabolism		(Li & Burmeister 2009; Li et al. 2003)
Non-alcohol substance use disorders		
Novelty seeking		(Sher et al. 2000)
Prefrontal cortex		(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)
Price promotions		(National Cancer Institute 2008; World Health Organisation 2012)
Receptors	Cholinergic	(Agrawal et al. 2012; Li & Burmeister 2009; Li et al. 2003; Liu et al. 2010; Thorgeirsson et al. 2010)
	CYPs	(Agrawal et al. 2012; Li & Burmeister 2009; Thorgeirsson et al. 2010)
	Glutamate	(Kalivas & O'Brien 2008; Xi & Stein 2002)
	Nicotinic	(Changeux 2010; Wilking et al. 2010)
	Opioid	(Koob 2006)
Reward processing		(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)
Route of consumption/ delivery		(McCambridge & Strang 2004; Ritter et al. 2006)
Social acceptance/ stigmatisation		(Gmel et al. 2010;Hallgren et al. 2012;Livingston et al. 2010;Partanen, 1991)
Unemployment		(Fergusson et al. 2006; Henkel 2011)
Ventral striatum		(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)

Cannabis

Determinants	References
Affordability	(Pacula 2010)
Criminalisation	(Campbell & Shaw 2008; Kolind et al. 2013; Levine & Small 2007; Stover & Michels 2010)
Depression	(Wittchen et al. 2007)
Drug driving	(Mark et al. 2012)
Early age at alcohol use onset	(Behrendt et al. 2011)
Early age at cannabis use onset	(Behrendt et al. 2011)
Early age at nicotine use onset	(Behrendt et al. 2011)
Early positive reactions to use	(Fergusson et al. 2006)
Economic downturn	(Arkes 2007; Chalmers & Ritter 2011)
Ethnicity	(Levine & Small 2007)
Externalising disorders	(Lee et al. 2011)
Generalised anxiety disorders	(de Dios et al. 2010)
Implicit cognitions	(Stacy & Wiers 2010; Wiers et al. 2013)
Lack of secure environment for use	(Dahl 2008b)
Legality/legal limits	(Nutt 2012; Schrager et al. 1991)
Personal alcohol use	(Caulkins & Nicosia 2010)
Prefrontal cortex	(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008b; Renthal & Nestler 2009)
Receptors	(Hall et al. 2001; Koob 2006)
Reward Processing	(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)
Route of consumption/ delivery	(Swift et al, 2000)
Sex	(Kendler KS 2003; Verweij et al. 2010)
Social acceptance/ normalisation	(Becker 1963; Measham et al. 1994)
Social anxiety	(Buckner et al. 2008)
Stigmatisation	(El Marroun et al. 2008; Schaub et al. 2010)
Stress	(Cougle et al. 2011; El Marroun et al. 2008)
Unemployment	(Henkel 2011)
Ventral striatum	(Kalivas & Volkow 2011; Maze & Nestler 2011; Renthal & Nestler 2008a; Renthal & Nestler 2009)

Stimulants

Determinants	References
Affordability	(Chaloupka & Pacula 1999; Grossman 2005; Markowitz 2005)
Availability	(Beckerleg et al. 2005)
Criminalisation	(Campbell & Shaw 2008; Kolind et al. 2013; Levine & Small 2007; Stover & Michels 2010)
Cue reactivity	(Volkow & Muenke 2012; Volkow et al. 2006; Wong et al. 2011)
Drug driving	(Stoduto et al. 2012)
Economic downturn	(Arkes 2007; Chalmers & Ritter 2011)
Ethnicity	(Levine & Small 2007; Schrager et al. 1991)
Impulsivity	(Verdejo-Garcia et al. 2008)
Lack of access to drug services	(Bourgois et al. 1997a; Burris et al. 2004; Castro & Singer 2004)
Lack of secure environment for use	(Dahl 2008a)
Legality/legal limits	(Nutt 2012; Schrager et al. 1991)
Low education	(Schrager et al. 1991; Van Ness et al. 2004)
Low housing stability	(Van Ness et al. 2004)
Low income	(Schrager et al. 1991)
Metabolism	(Tsuang et al, 2001;Agrawal and Lynskey, 2008;Agrawal et al, 2012)
Prefrontal cortex/ ventral striatum	(Everitt and Robbins, 2005; Russo et al, 2010;Badiani et al, 2011; Kalivas and Volkow, 2011)
Receptors	(Meaney et al., 2002;Volkow et al, 2004;Nader et al, 2006; Leyton, 2007;Martinez et al., 2009;Ghitza et al., 2010)
Reward processing	(Everitt and Robbins, 2005; Russo et al, 2010;Badiani et al, 2011; Kalivas and Volkow, 2011)
Route of consumption/ delivery	(Mathers et al. 2008)
Social acceptance/ normalisation	(Yinger, 1960; Parker et al, 1998; 2002;Moore, 2004;Sznitman, 2007)
Stigmatisation	(Christie and Bruun, 1985;Room et al, 2001;Room, 2005;McCabe, 2008;Jöhncke, 2009)
Stress	(Meaney et al, 2002)
Unemployment	(Henkel 2011)

Opioids

Determinants	References
Affordability	Saffer and Chaloupka, 1999;Van Ours, 1995;Liu et al, 1999;Dave, 2008)
Availability	(Beckerleg et al, 2005)
Criminalisation	(Levine and Small, 2007;Campbell and Shaw, 2008;Frank and Kolind, 2008;Stöver and Michels, 2010)
Economic downturn	(Ben Lakhdar and Bastianic, 2011)
Ethnicity	(Schrager et al, 1991)
Impulsivity	(Verdejo-Garcia et al, 2008)
Lack of a secure environment for use	(Dahl, 2008)
Lack of access to drug services	(Burris et al, 2004;Castro and Singer, 2004; Bourgoiset al, 2007)
Legality/legal limits	(Nutt et al. 2007)
Low education	(Schrager et al. 1991; Van Ness et al. 2004)
Low housing stability	(Van Ness et al. 2004)
Low income	(Schrager et al. 1991)
Metabolism	(Agrawal and Lynskey, 2008;Agrawal et al, 2012)
Prefrontal cortex/ Ventral striatum	(Everitt and Robbins, 2005; Russo et al, 2010;Badiani et al, 2011; Kalivas and Volkow, 2011)
Receptors	(Bonci and Williams, 1997; Bart et al., 2004; 2005;Glatt et al, 2007; Badiani et al., 2011;Kreek et al, 2012)
Reward processing	(Everitt and Robbins, 2005; Russo et al, 2010;Badiani et al, 2011; Kalivas and Volkow, 2011)
Route of consumption/ delivery	(Mathers et al. 2008)
Social acceptance/ normalisation	(Yinger, 1960; Parker et al, 1998; 2002;Moore, 2004;Sznitman, 2007)
Stress	(Walter et al, 2013)
Unemployment	(Henkel 2011)

Club drugs

Determinants	References
Availability	(Fitzgerald, 2002)
Branding	(Fitzgerald, 2002)
Criminalisation	(Levine and Small, 2007;Campbell and Shaw, 2008;Frank and Kolind, 2008;Stöver and Michels, 2010)
Impulsivity	(Verdejo-Garcia et al, 2008)
Lack of a secure environment for use	(Dahl, 2008)
Lack of access to drug services	(Burris et al, 2004;Castro and Singer, 2004; Bourgoiset al, 2007)
Legality/ legal limits	(Nutt et al. 2007)
Metabolism	(Agrawal and Lynskey, 2008)
Prefrontal cortex/ ventral striatum	(Everitt and Robbins, 2005; Russo et al, 2010;Badiani et al, 2011; Kalivas and Volkow, 2011)
Receptors	(Sora et al, 2010)
Reward processing	(Everitt and Robbins, 2005; Russo et al, 2010;Badiani et al, 2011; Kalivas and Volkow, 2011)
Route of consumption/ delivery	(Mathers et al. 2008)
Social acceptance/ normalisation	(Yinger, 1960; Parker et al, 1998; 2002;Moore, 2004;Sznitman, 2007)
Stigmatisation	(Christie and Bruun, 1985;Room et al, 2001;Room, 2005;McCabe, 2008;Jöhncke, 2009)

Gambling

Determinants	References
Accessibility	(Griffiths et al. 2003)
Anxiety disorders	(Blaszczynski and Nower, 2002;Lorains et al, 2011)
Availability	(Ladouceur et al, 1999; Sharpe, 2002;Abbot et al, 2004;Barnes et al, 2004;King et al, 2010;Hodgins et al, 2011)
Cognitive distortions	(Blaszczynski and Nower, 2002; Abbot et al, 2004;Delfabbro, 2004; Ladouceur, 2004; Parke and Griffiths, 2006; Clark, 2010; Hodgins et al., 2011)
Coping mechanisms	(Johansson, 2006; Stewart et al, 2008;Johansson et al, 2009;Myrseth et al, 2009; Nelson et al, 2009;Shead et al., 2010;Yi & Kanetkar, 2011)
Divorced/separated/widowed marital status	(Petry et al, 2005; Hodgins et al., 2011)
Early age of onset	(Volberg et al, 2001;Petry et al, 2005; Johansson, 2006; Shead et al, 2010; Hodgins et al, 2011)
Ethnicity	(Welte et al, 2004; Petry, Stinson, & Grant, 2005; Alegria et al, 2009;Hodgins et al., 2011)
Externalising disorders	(Grall-Bronnec et al, 2011)
High event frequency	(Parke and Griffiths, 2006)
High jackpot size	(Parke and Griffiths, 2006)
Impulsivity	(Alessi & Petry, 2003; Chambers & Potenza, 2003; Blanco et al., 2009; Johansson, 2006;Johansson et al., 2009; Myrseth et al., 2009; Dussault et al., 2011; Liu et al., 2013)
Lack of clocks	(Griffiths, 2011)
Legality/legal limits	(Grant & Potenza 2007)
Light/colour/sound effects	(Parke and Griffiths, 2006)
Low education	(Welte et al, 2004;Afifi et al, 2010)
Low income	(Welte et al, 2004;Afifi et al, 2010)
Low social class	(Welte et al, 2004)
Maintenance of light levels	(Griffiths, 2011)
Male gender	(Blanco et al, 2006; Johansson, 2006; Afifi et al, 2010;Shead et al, 2010;Hodgins et al, 2011)
Mood disorders	(Blaszczynski & Nower, 2002; Afifi et al, 2010;Hodgins et al, 2011;Lorains et al, 2011; Dussault et al, 2011)
Nicotine dependence	(Lorains et al, 2011)
Prefrontal cortex/ ventral striatum	(Comings et al., 2001;Reuter et al., 2005; Verdejo-García et al, 2008;Van Holst et al, 2012)
Promotion	(Afifi et al, 2010)
Receptors	(Guo et al, 2009)
Reward processing	(Comings et al., 2001;Reuter et al., 2005; Verdejo-García et al, 2008;Van Holst et al, 2012)
Short payout intervals	(Parke and Griffiths, 2006)
Social acceptance/ normalisation	(Gmel et al. 2010; Hallgren et al. 2012; Livingston et al. 2010; Partanen 1991; Room 2007; Room & Makela 2000; Rootman & Moser 1984; Skog 1985; Weisner & Schmidt 1995)
Stress	(Lorains et al, 2011)
Substance use disorders	(Lorains et al, 2011)
Visible near miss features	(Parke and Griffiths, 2006)
Waitress service of food and drink	(Griffiths, 2011)

APPENDIX 3: Stimulants model with multidisciplinary emphasis