Animal models of binge drinking, current challenges to improve face validity

Jérôme Jeanblanc, Benjamin Rolland, Fabien Gierski, Margaret Martinetti, Mickaël Naassila

Animal models of binge drinking, current challenges to improve face validity

Jérôme Jeanblanc [a], Benjamin Rolland[b], Fabien Gierski[a,c], Margaret P. Martinetti[d], Mickael Naassila[a,*],

[a] *INSERM U1247; GRAP; CURS; Univ Picardie Jules Verne, Amiens, France. E-mails: mickael.naassila@inserm.fr jerome.jeanblanc@u-picardie.fr*

[b] *UCBL; CRNL; INSERM U1028; CNRS UMR5292; Univ Lyon, Lyon, France, and Service Universitaire d'Addictologie de Lyon (SUAL), Pôle UP-MOPHA, CH Le Vinatier, Bron, France. E-mail: benjamin.rolland@univ-lyon1.fr*

[c] *Laboratoire Cognition Santé Société (C2S - EA 6291), Reims Champagne-Ardenne University, Reims, France. E-mail: fabien.gierski@univ-reims.fr*

[d] *Department of Psychology, The College of New Jersey, Ewing, NJ. E-mail:* martinet@tcnj.edu

** Corresponding author / Department contact: Prof. Mickael Naassila, Université de Picardie Jules Verne, INSERM U1247 – Research Group on Alcohol & Pharmacodependences (GRAP) – CURS – Chemin du Thil 80025 Amiens cedex 1 - +33322827672. E-mail: mickael.naassila@inserm.fr*

Running Head: Animal models of binge drinking

Word count: 6405

Number of Figures: 6 Number of Tables: 1 Number of References: 115

Key words: binge drinking; animal models; rodents; validity; alcohol

List of abbreviations

BEC – Blood Ethanol Concentration

BD – Binge Drinking

DID – Drinking In the Dark

NIAAA – National Institute on Alcohol Abuse and Alcoholism

1. Introduction

1.1 Definition and diagnostic of BD in humans

Binge drinking (BD) refers to a specific pattern of alcohol use, namely drinking large amounts of alcohol in a short period of time (Courtney and Polich, 2009). The BD behavior is characterized by the intensity and also by the frequency of the drinking episodes and BD behavior is thus including longer or shorter periods of no consumption (between binges) (SAMHSA, 2016).These periods of abstinence, among other criteria such as the loss of control over alcohol consumption and the compulsion, allow the distinction between BD and some other patterns of unhealthy alcohol use, especially severe alcohol dependence (Rolland and Naassila, 2017) in which daily alcohol consumption is usually observed. For this reason, BD is frequently defined as an “episodic heavy use of alcohol” (WHO, 2014; SAMHSA, 2016).

In the epidemiological literature, the criteria for BD include exceeding drinking thresholds in a short amount of time. For example, the World Health Organization (WHO) defines BD as the "*consumption of 60 or more grams of pure alcohol (6+ standard-drinks in most countries) on at least one single occasion at least monthly*" (WHO, 2014). However, the National Institute on Alcoholism and Alcohol Abuse (NIAAA) defines BD as "*a pattern of drinking alcohol that brings blood alcohol concentrations to 0.08 gram percent or above. For the typical adult, this pattern corresponds to consuming five or more drinks (male)* [American drinks, i.e., 14g of ethanol]*, or four or more drinks (female), in about two hours*" (NIAAA, 2017, (Courtney and Polich, 2009)). Compared with the WHO definition, the NIAAA definition of BD also involves a minimum drinking speed and deliberately seeking drunkenness. Consequently, these two common definitions of BD convey subtle conceptual differences, and the epidemiological populations that they delineate do not display the same clinical profile and severity level (Rolland et al., 2017). Moreover, the typical definitions of BD do not explore the frequencies of drinking or heavy drinking behaviors, or the average amount of alcohol used during BD episodes but rather focus on the thresholds described in the different definitions and thus define BD groups (above the threshold) and non BD groups (below the threshold). As the severity of BD can directly depend on these parameters, BD populations studied using the usual definitions only are actually very heterogeneous, which raises some important scientific concerns (Ceballos and Babor, 2017, Rolland and Naassila, 2017). In this regard, a recent study has shown that, compared with the WHO criteria, the NIAAA criteria for BD identifies individuals with more severe drinking patterns and alcohol consequences (Rolland et al., 2017).

Taking a mere drinking threshold to define such a complex behavior like BD can lead to the undescreening people that are drinking with an intensity that is very far from this threshold and thus display very specific and important characteristics (regarding drinking behavior and personality). To this end, in its recent newsletter (NIAAA Spectrum, 2017) the NIAAA refers to the study of Hingson and White (Hingson et al., 2017) that proposes new cut-offs of ethanol consumed in a single occasion (for women and men, respectively): level I (56-98g and 70-126g), level II (112-154g and 140-196g), and level III (>168g and >210g). They also defined levels II and III (i.e., exceeding 112g and 140g in a single occasion for women and men, respectively) as "extreme binge drinking."

Although these thresholds account for the heterogeneity of the behavior, they do not address the frequency of the behavior. For example, an individual who has had one panic attack in the past month may indeed have panic disorder, but the *recurrence* of attacks (as well as other criteria) are needed for the diagnosis of this disorder. Therefore, valid definitions of BD require not only specific features of the drinking patterns, such as drinking intensity per drinking occasion, but also frequency of BD behaviors and periods of abstinence between binging episodes. Moreover, recent data suggest that BD is a heterogeneous phenotype. Consequently, binge drinkers should not be considered as a unitary group, but rather as a heterogeneous population of individuals displaying particular gender and personality dimensions (Gierski et al., 2017), as well differences in drinking motives and impulsivity (Lannoy et al., 2017a).

In an attempt to provide a more behavioral definition of BD, Townshend and Duka (2002) proposed the computation of a "binge score," which is based on both the frequency of excessive consumption and the average speed of consumption

(Townshend and Duka, 2002, Smith et al., 2017). In one application of this measure, participants with a history of BD had more severe brain damage and cognitive impairment compared with social drinkers, and the degree of these impairments was positively correlated with the binge score (Smith et al., 2017).. Such findings revealed that both the level of intoxication and drinking speed (producing higher binge score) were crucial factors in the impact of BD behavior (Smith et al., 2017). In particular, fast alcohol consumption, especially on an empty stomach, allows ethanol to reach the blood more rapidly, and increases blood alcohol levels with a life-threatening speed. “Happy hours”, during which alcoholic drinks are cheaper for a limited period of time, dramatically promote BD behavior and severe intoxication (Thombs et al., 2008), and new policies have emerged to curb BD. Inspired by human anecdotal evidence and the culture of “happy hours,” animal models have evolved to mimic BD by shortening the access to alcohol.

Animal models are meant to parallel the human condition; however, rodents do not readily consume sufficient amounts of ethanol to achieve pharmacologically relevant blood ethanol concentrations (BEC) if they have not been genetically selected for their high ethanol preference or exposed to ethanol during early life (*in utero* or at adolescence) (Alaux-Cantin et al., 2013, McBride et al., 2014). Despite these challenges, the present article presents new evidence indicating that a rodent model of BD is now possible. Such models allow greater control over environmental parameters, and thereby enable systematic testing of those individual and environmental factors that may promote voluntary BD behavior. Ultimately, animal models of BD will address identification of neurobiological factors and how the speed of drinking may be the keystone factor in this behavior.

Although the number of publications on “BD in students” has increased since the beginning of the 1990’s, the same increase among comparable papers describing animal models of BD began around 2010 (see Figure 1). Since 2008, more than 120 preclinical studies on BD have been published each year essentially on either rats or mice, but clearly, the animal literature has not kept pace with the burgeoning research on BD in students.

1.2. Relevant clinical criteria for developing animal models of BD

The specific behavioral pattern of BD is central to the development of an animal model of BD. Thus, the quantity, frequency, and duration parameters are crucial. Concerning quantity, signs of intoxication (such as motor impairment, which is the most easily visible sign of intoxication in rodents) must be achieved with a sufficient amount of alcohol consumed in a short period of time. Even though intoxication is not part of the clinical definition, pharmacologically relevant BECs of approximately 1g/l need to be achieved, especially because rodents metabolize alcohol much more rapidly than humans (in rats, 3 times greater, or 300mg/kg/h and in mice, 5.5 times greater, or 550mg/kg/h). Figure 2 depicts BEC magnitude and time-course in humans, rats and mice after binge-like ethanol administration of about 0.5 to 0.75g/kg, and illustrates that rodents metabolize ethanol faster than humans. With respect to frequency and thus the history of the BD behavior in humans, this factor is very heterogeneous depending on the studies. For example, some studies investigated the BD behavior during the past month, the past 6 or 12 months or other durations before the recruitment. Furthermore, only few studies report dependence as an exclusion criterion in the BD studies, this should be clarified because BD and dependence are two different entities at the nosographical level. The BD behavior is more characterized by episodic drinking (intermittent consumption interspersed with

longer or shorter periods of non-consumption) while dependence is more reflected by a daily consumption. Recently, in one study focusing on BD in humans (Morris et al., 2018) dependence was an exclusion criterion. In addition, in our previous study on BD in humans (Rolland et al., 2017), in the absence of DMS-5 diagnostic, a daily heavy consumption of alcohol, closely related to dependence diagnostic was also considered an exclusion criterion. This distinction is actually ambiguous since only very few studies on BD evaluated the dependence criterion and on the same vein, very few study studying dependence focused on BD patterns. Consideration of dependence in BD studies is important because it is also possible that a certain proportion of binged drinkers may be already dependent.

The frequency of BD is in fact important to consider, since different populations of binge drinkers can be distinguished according to this parameter, e.g., “frequent” or “infrequent” binge drinkers and animals can thus be used to model either the impact of very few or that of repeated BD episodes. The frequency of BD and individual history are important since chronic BD (i.e., for several months or years) is a risk factor for alcohol addiction in humans (Kuntsche et al., 2017). Moreover, it is frequently not clear whether participants in the clinical population recruited for BD studies met criteria for dependence (although this diagnosis has been removed from the DSM-5) (Rolland and Naassila, 2017). Finally, the duration, or the time period over which drinking occurs, is the most important parameter to identify BD because given equal quantities consumed, heavy drinking becomes BD as duration shortens.

Underage BD is a major health concern in several countries. Thus, using a developmental approach with animal models of BD could determine the mechanisms underlying long-term vulnerability for alcohol dependence. For example, several rodent studies have used forced and repeated (intermittent) ethanol administration

during the adolescence period in rodents (the second month of life). This research has showed that increased risk for consuming alcohol in adulthood may involve reward deficit syndrome (Alaux-Cantin et al., 2013). Interestingly, it has been shown that intermittent access to voluntary ethanol drinking facilitates excessive drinking after rats are subsequently exposed to chronic intermittent ethanol vapor (Kimbrough et al., 2017). Thus, the frequency and the pattern of alcohol drinking may play a crucial role in vulnerability to dependence.

Clinical studies have shown that BD is associated with impairment in executive function, such as inhibitory control and decision-making (Lannoy et al., 2017b). BD is also associated with alterations in grey and white matter that are correlated with cognitive impairments (Hermens et al., 2013). Interestingly some results have revealed that BD is associated with impaired performance on cognitive tasks in women more than men (Townshend and Duka, 2005). Thus, both brain alterations and cognitive impairments (e.g. in prefrontal executive functions or memory) must be investigated in animal models of BD, and differences linked to gender, as well as interactions between BD and gender differences in brain maturation, should be explored. At the somatic level, some studies suggest that BD, independently of daily alcohol intake, can lead to more severe forms of alcoholic liver disease in younger populations (Ventura-Cots et al., 2017).

2. Current preclinical models of BD

Preclinical research on alcohol also suffers from this lack of a clear definition of BD behavior. Animal models attempt to parallel the human condition, and in fact, the NIAAA definition of BD in humans has been used in animal studies (Crabbe et al., 2011a).

Published studies on BD using the nonhuman primate model are scarce. Adolescent nonhuman primate model has been used to investigate the impact of BD on hippocampal neurogenesis using oral ethanol self-administration induced with a procedure in which the concentration of ethanol in a palatable solution (Tang) was gradually increased (1 to 6%) over a series of daily limited-access sessions (1-h) for 11 months (Taffe et al., 2010.). In this model nonhuman primates consumed an average of 1.74g/kg of alcohol during the 1-h daily sessions and they reached BEC of 50 to 300 mg/dl when measured 30min after the beginning of the session. Another study in primate model on the transgenerational effects of BD used a forced administration of increasing doses (0.75 to 1.5 g/kg) of ethanol (mean BEC at 3-h post administration of 140.3±31.3 mg/dl) via nasogastric tube twice weekly for 6 months (VandeVoort et al., 2015).

In the present review we have chosen to focus on rodent models of BD for which we have the most data compared to other species.

Current animal models of BD can be divided into two large categories depending on the mode of administration: forced/passive administration of high alcohol doses or voluntary/active alcohol consumption.

2.1. Forced administration of high doses of alcohol

In this first category, animals receive high doses of alcohol solution leading to rapid elevation of BEC and clear signs of intoxication. These procedures are easy to perform and do not require the acquisition of specific equipment; however, as we will discuss later, the passive administration of a drug does not produce the same neurobiological and behavioral modifications as voluntary consumption, and therefore, may be of limited use, depending on the scientific question.

2.1.1. Gavage:

This simple procedure consists of the insertion of a guide cannula into the esophagus of the rodent and the injection of an ethanol solution (usually a 10 or 20 % ethanol solution in tap water). Through absorption in the digestive tract, BEC will increase rapidly, reflecting the pharmacokinetics observed in humans (Yang et al., 2001). With a single administration, BECs can reach more than 500 mg/dL, sustained for several hours, after a gavage of 7g/kg (32% ethanol solution v/v) (Carson and Pruett, 1996). In mice, more moderate and ecologically valid BECs generally are produced (e.g., 120 mg/dL for 30 minutes after a gavage of 1.12g/kg of a 10% ethanol solution) (Chen et al., 2013). Major differences exist between mice and rats using the gavage procedure. For example, 300 and 100 mg/dL are achieved after a gavage of 3.8 g/kg of a 21% ethanol solution in mice and rats, respectively (Livy et al., 2003). Mice show a faster rise and higher peak BEC and elimination rates while rats show more gradual pharmacokinetics profiles and retain ethanol in their bloodstream for longer periods (Figure 2). The gavage procedure can be performed acutely (Jin et al., 2017, Liu et al., 2017) or in subchronic (Thompson et al., 2017) and chronic procedures (Hansen et al., 2017), but with the limitation that the direct administration of large volume of an ethanol solution in the stomach will induce direct damage to the organ (Kawashima and Jerzy Glass, 1975, Chen et al., 2013). In addition, the repeatability of the results are dependent of the gastric contents at the time of administration, and it has been well described that ethanol administration by gavage will have different consequences (absorption, pharmacokinetic, BECs reached, behavioral consequences) when the stomach is empty or not (Roine et al., 1991). Thus, the gavage procedure has limited utility to investigate BD (Livy et al., 2003, Walker and Ehlers, 2009). Although a large variety of studies on liver injury has

been performed using this paradigm (Thompson et al., 2017, Wang et al., 2017, Yao et al., 2017), fewer studies have used it in behavioral neuroscience (Griffin et al., 2009, Anton et al., 2017, Karelina et al., 2017). Nevertheless, some utility of the gavage procedure has been recognized because a combination of the Lieber-DeCarli regimen (forced consumption of alcohol through the sole source of nutrients) and the gavage procedure have been recently identified as the NIAAA model of chronic and binge ethanol feeding (Bertola et al., 2013a, Bertola et al., 2013b).

2.1.2. Intra-peritoneal injections:

This procedure is easier to implement than the gavage, partially because intra-peritoneal injections may induce less stress than the gavage procedure. There are also large differences between rats and mice using the intra-peritoneal route, and like gavage, the peak BECs are lower in rats than in mice (Livy et al., 2003). Most of the time, these procedures are used acutely and sometimes sub-chronically with a specific schedule of administration, and single or multiple discrete injections of alcohol have been used extensively to study the effect of acute intoxication in rodents. Moderate to high doses (i.e., around 2 to 3 g of pure ethanol/kg of body weight for the mice and 1.5 to 3g/kg for the rats) are typically tested in order to induce intoxication without sedative/hypnotic effects (measured with the loss of the righting reflex). In the Naassila laboratory, we have used a protocol of 2 consecutive injections of ethanol administered 9 hrs apart to mimic a double binge-like episode and to determine if only two BD episodes are sufficient to adversely affect memory and synaptic plasticity. Indeed, using this procedure in adolescent rats, Silvestre de Ferron and colleagues (Silvestre de Ferron et al., 2015) demonstrated that only 2 intoxications induced by injections of 3g/kg of ethanol, lead to a complete deletion of the specific form of synaptic plasticity called long-term depression. The abolition of

this specific form of synaptic plasticity may be responsible for a perturbation of memory processes assessed in the novel object recognition test. Several variants of this procedure can be found in the literature. For example, Pascual et al. (Pascual et al., 2007) developed a relevant protocol in which rats received a total of 8 intra-peritoneal injections following a schedule of 1 daily injection for 2 days in a row, then 2 days off, and so on, until rats received the 8 injections of a 25% ethanol solution at a dose of 3 g/kg. This protocol mimics BD-like ethanol exposure during the adolescent period (postnatal day 25 to 38) as observed in humans and also to introduce withdrawal-like period with the 2-day off intervals. This protocol has also been successfully used in mice with identical injections from postnatal 30 to 43 (Pascual et al., 2017b) to study inflammatory mechanisms following binge-like exposure. Pascual et al. (2007) found that this pattern of alcohol injections leads to behavioral alterations (evaluated in a conditioned discrimination learning task) and is associated with brain damage linked to apoptosis and neuroinflammation. Numerous studies have now been published using this procedure (Pascual et al., 2012, Alaux-Cantin et al., 2013, Montesinos et al., 2016).

One of the limitations of these intra-peritoneal injections of alcohol procedures is the local pain and irritation induced by the injection of a large volume of a solution of ethanol (10 to 20% usually). Repetition of injections may result in an increase of stress and local inflammation associated with damages to different organs (D'Souza El-Guindy et al., 2010).

2.1.3. Inhalation of alcohol vapors:

The alcohol vapor inhalation model was developed to induce physical signs of alcohol dependence by arranging long intoxication periods for several weeks or

months, with target BECs of 175–250 mg/dL (Le Bourhis, 1975, Le Bourhis and Aufrere, 1983, Schulteis et al., 1995, Simon-O'Brien et al., 2015). More recently, and to better model the observed pattern of alcohol consumption in humans with alcohol addiction, intermittent exposure has been introduced every day (usually 14h on/10h off per day). These durations of intoxication seem too long to be associated with binge-like intoxication. To our knowledge, short periods of exposure to ethanol vapors have not been used to mimic BD.

2.1.4. Forced drinking:

For this procedure, rats or mice are kept usually in their home cage and instead of having water delivered *ad libitum*, alcohol is the sole source of fluid. Thus, rodents have to drink the alcohol solution to survive. The scheduled high alcohol consumption is another paradigm in which availability of water is restricted; in order to survive, rats must drink more ethanol as a function of reduced access to water (Cronise et al., 2005). Another forced consumption of alcohol can be obtained using a liquid diet procedure developed by Lieber and DeCarli (Lieber and DeCarli, 1975). Rodents have access to a bottle containing ethanol (4 to 9 % w/v) and all the necessary nutrients for several weeks. Intoxicating levels are easily reached (100 mg/dL in Wistar rats, (Weiss et al., 1996) and until 180 mg/dL in C57 mice (Bertola et al., 2013a). Despite the somewhat forced nature of consumption, bouts are titrated over a 24-h period and to our knowledge no study has demonstrated that rats could display BD-like behavior using this procedure when ethanol solution is available 24-h a day and not only during a restricted period of time of the day. However, using these procedures, rats can consume more than 7g/kg ethanol/day, thereby exceeding their daily ethanol metabolism capacity (Aufrere et al., 1997). It is of note that forced drinking may be linked to a reduction in daily total fluid intake depending on the strain

(Azarov and Woodward, 2014) which may have moderate dehydration consequence (Blank et al., 1991) leading to stress and thus altering behavioral and physiological parameters.

2.1.5. Summary of the studies on ethanol forced administration

All of the forced-ethanol administration procedures described above have the ability to induce alcohol intoxication and allow the researchers to observe direct consequences of binge-like intoxication. In addition, they are simple to set up in all laboratories, with no need for expensive equipment, and can rapidly generate experimental animals displaying high level of ethanol intake. Following such procedures, several types of experiments can be performed, such as genetic testing (Pascual et al., 2007), behavioral studies (Montesinos et al., 2016), neuroinflammation investigation (Pascual et al., 2015), in addition to study of the microbiota (Chen et al., 2015) and liver injury (Wilkin et al., 2016). However, these paradigms are limited as models of human BD because consumption cannot be viewed as voluntary. Therefore, it is difficult, or even impossible, to evaluate some important parameters of drug consumption such as the motivation to consume and the seeking for the drug in a non-operant paradigm. Finally, even though the gavage procedure (i.e., via the oral route) may appear to have greater face validity compared with the intra-peritoneal route, it should be considered that, at least in rats, its ability to mimic BD is limited since the achieved peak BECs and alcohol elimination rates are low.

2.2. Voluntary alcohol consumption

In contrast to forced alcohol administration, voluntary alcohol consumption usually does not result in sufficient levels of BEC to induce any behavioral signs of

intoxication, at least in outbred animals that have not been genetically selected for their ethanol preference. Recently, several protocols, mostly in mice and sometimes in rats, have been developed to induce high levels of BEC. One long-standing method that has been used successfully to enhance voluntary alcohol intake is the scheduling of alcohol availability (Le Magnen, 1960). When animals have unlimited access to alcohol, the consumption bouts are usually titrated over a 24-h period. Thus, even though significant pharmacologically relevant BEC may be obtained at some points during the day, animals do not display visible signs of motor impairment. Therefore, other models have been developed to achieve elevated BECs in different periods of time.

2.2.1. 20% alcohol intake in the two-bottle choice intermittent access model:

In 1973, Roy Wise described a protocol of voluntary alcohol consumption using a 2-bottle-choice paradigm in which rats have access to one bottle of tap water and one of alcohol (20% ethanol solution) every other day (Wise, 1973). Using this protocol, rats demonstrate increased consumption, leading to alcohol intake of more than 5g/kg per day when alcohol is available. Interestingly, a recent study revealed that multiple episodes of excessive alcohol consumption using this model (3 days per week for 7 weeks) leads to somatic damage measured as liver metabolism dysfunction and inflammation (Wegner et al., 2017). This procedure found a new revival in the beginning of the 2000s with several publications (Simms et al., 2008, Carnicella et al., 2009, Hopf et al., 2010, Simon-O'Brien et al., 2015, Spoelder et al., 2017a, Spoelder et al., 2017b). A major advantage of this procedure is that it can be performed with inbred animals, such as Fischer rats, (Mill et al., 2013) and C57BL/6J mice (Hwa et al., 2011) and alcohol-preferring lines including the Sardinian P rats (Sabino et al., 2013), as well as with outbred rats such as Long Evans (Carnicella et

al., 2008, Ben Hamida et al., 2012, Meyer et al., 2013), Wistar (Wise, 1973, Simms et al., 2008, Hopf et al., 2010, Cippitelli et al., 2012) and Sprague-Dawley rats (Bito-Onon et al., 2011). This procedure is normally used to study long-term alcohol consumption over a 24-h period; however, animals will consume a large part of their daily total intake only during the first hours of presentation of the alcohol bottle. Depending on the laboratory, the duration of this binge-like consumption is measured during the first 30 minutes (Simms et al., 2008, Carnicella et al., 2009, Ben Hamida et al., 2012), the first hour (Sabino et al., 2013) or the first two hours (Hwa et al., 2011). The total amount of ethanol consumed during the first 30 minutes represents at least 20% of the total amount consumed in 24-h and leads to averaged BECs of 80 mg/dL with some animals showing BECs above 100 mg/dL (Carnicella et al., 2009). Similar results were obtained with the Sardinian P rats with an average BEC around 80 mg/dL but with only very few animals reaching more than 100 mg/dL after 1-h of consumption (Sabino et al., 2013). In their elegant study, Simms et al., compared different strains of rats and showed that in 30-min, the Long Evans rats exhibited higher BECs and higher interindividual variability than Wistar and P rats (Simms et al., 2008). Thus, their results suggest that the Long Evans may be most suitable for BD studies.

The predictive validity of this BD model has also been demonstrated. Indeed naltrexone decreased the total amount of alcohol consumed during the first 30 min of the drinking episode from 1.1 to 0.6 g/kg/30 min (Simms et al., 2008). Moreover, varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist already used in smoking cessation leads to a decrease in ethanol consumed in this model from 1.4 to 0.4 g/kg/30 min (Steensland et al., 2007).

In this 20% ethanol intermittent access model, the escalation of ethanol intake may be associated with sensitization since it develops in a few weeks and then reaches a plateau, and once established, can last even after 40 days of ethanol intake discontinuation (Simms et al., 2008). This point is very interesting in the context of BD behavior since it reflects the fact that episodic ethanol intake may profoundly impact brain functioning and therefore, behavior.

2.2.2. Two bottle choice drinking-in-the-dark model:

Currently, the most frequently used model to mimic BD is the drinking-in-the-dark (DID) procedure, in which animals drink large amounts of ethanol during the first hours of the dark cycle, either immediately upon lights out (for rats) or after 3 or 4 hours (for mice) and display BEC in excess of 0.8g/L (Thiele et al., 2014). There are several variations on the DID model, depending on the laboratory performing the experiment: some use a one-bottle paradigm (Rhodes et al., 2005, Crabbe et al., 2009, Neasta et al., 2010), others a 2-bottle paradigm (Kaur and Ryabinin, 2010, Burnham and Thiele, 2017), and even some others a 4-bottle choice paradigm (Colombo et al., 2014). Similarly, the time of the beginning of the drinking sessions within the dark phase can vary from 1 to 4 hours and the duration of the drinking episode can be of 2 to 4 hours (Rhodes et al., 2005). The major caveat of this procedure is that it seems to produce intoxicating levels only in inbred animals known to show spontaneous alcohol preference. Indeed, the same group of researchers demonstrated that this DID model leads to intoxication (BECs > 80 mg/dL) only in C57BL/6J mice when compared with 11 other strains of mice (Rhodes et al., 2007). In a recent study using the Sardinian P rats, Colombo et al. (2014) demonstrated that the start time of the drinking phase plays a role in the amount of alcohol consumed in a 4-bottle choice paradigm. Indeed if the session of drinking starts 1 hour prior to the

end of the dark phase of the day, rats will consume 3 times more alcohol than if the session starts at the beginning of the dark phase. The rats consumed up to 2g/kg of pure ethanol in 1 hour, thereby leading to intoxication (BECs around 100 mg/dL) and symptoms of such intoxication revealed by rotarod impairment (Colombo et al., 2014).

A multiple scheduled access (MSA) has been added to the DID procedure in which animals experience between two and four-hour access periods across the 12-h dark cycle with each access period separated by 2 or more hours. However, this DID-MSA procedure has been used mainly in alcohol-preferring rats (Bell et al., 2009, McBride et al., 2010) and not outbred animals, and thus, it does not allow for generalization to highly heterogeneous populations. One other caveat of this procedure is that it usually takes place within a week and thus does not allow the establishment of a robust chronic consumption of elevated levels of alcohol. One study using the DID procedure aimed to overcome this problem by providing access to the bottle for 6 weeks (Wilcox et al., 2014). The authors found that the consumption was stable over this extended period of DID. In addition, they found that this prolonged chronic binge-like consumption of alcohol led to neurobiological alterations, such as depressed GABAergic transmission and modifications of neuron excitability (frequency of discharge), with a shift from the dorsomedial striatum to an activation of the dorsolateral part of the striatum after a prolonged experience of DID in response to an acute administration of alcohol (Wilcox et al., 2014).

The predictive validity of the DID model was confirmed using naltrexone, one clinically recognized treatment for alcohol addiction, and also using the dopamine re-uptake blocker GBR 12909. Both drugs were able to dose-dependently decrease ethanol consumption in this model (Kamdar et al., 2007).

The DID procedure also has been used to create a selected mouse line, akin to the alcohol-preferring P rat. Crabbe and his colleagues selected over 11 generations of mice, called the High Drinking-in-the-Dark mice (HDID) exhibiting the highest levels of ethanol consumption in this procedure (Crabbe et al., 2009, Crabbe et al., 2011b). This selection produced average BECs above 100 mg/dL with a maximum of 250 mg/dL in 2 hours of consumption. The predictive validity of the HDID model was tested using 3 different actual drugs used to treat alcohol-dependent patients, namely naltrexone, baclofen and acamprosate. Surprisingly, the authors found that only acamprosate, and with a high dose, was able to reduce ethanol consumption in the HDID mice, but without significantly reducing the BECs, when consumption was evaluated for 4 hours (Crabbe et al., 2017). When evaluated in the 2 first hours, baclofen was able to reduce both alcohol consumption and subsequent BECs, but non-selectively, as it also reduced water intake (Crabbe et al., 2017). Because naltrexone was not effective in the HDID model, and relatively high doses of drugs were required to reduce consumption, the HDID model lacks sufficient predictive validity, particularly because naltrexone is known for its efficacy in reducing high level of alcohol intake in patients who relapse (Jonas et al. 2014).

2.2.3. Operant binge drinking:

Voluntary ethanol consumption in the 2-bottle choice paradigm can lead to intoxication, but otherwise, provides little information concerning complex alcohol-associated behaviors. Conversely, operant self-administration of alcohol has been widely used to obtain such type of information (motivation, seeking, relapse after extinction…); however, even with the combination of a 20% intermittent access protocol to induce alcohol palatability in outbred rats, the total amount of alcohol consumed barely reached the levels of intoxication in periods of 30 minutes

(Jeanblanc et al., 2009, Carnicella et al., 2011, Carnicella et al., 2014, Jeanblanc et al., 2015, Darcq et al., 2016).

Gilpin and colleagues have developed an operant model of binge-like alcohol self-administration in adolescent Wistar rats (Gilpin et al., 2012). By adding a mixed solution of 3% glucose/0.125% saccharin to a 10% ethanol solution (w/v), the authors observed intakes exceeding 1 g/kg/30 min leading to BECs around 80 mg/dL. Moreover, the rats exhibiting high levels of ethanol self-administration during adolescence showed reduced anxiety at adulthood.

We caution that the use of any type of sucrose should be avoided in animal models of excessive alcohol intake (Carnicella et al., 2014). Sweeteners may reduce blood ethanol levels for a particular volume of ethanol consumed (Roberts et al., 1999) and saccharin can alter the dynamics of cue-ethanol memory reconsolidation (Puaud et al., 2018). Sucrose-sweetened ethanol and sucrose fading are frequently used in animal models of operant oral self-administration, but researchers should be wary of possible interactions with neurobiological and behavioral outcomes (Carnicella et al., 2014).

Recently, we demonstrated that a daily, very short session of operant self-administration can facilitate the acquisition of BD behavior in rats (Lebourgeois et al., 2017) (Jeanblanc et al., 2018). After several weeks of training under a fixed ratio 3 (3 lever presses to get 0.1ml of 20% ethanol) during 1 hour, and thereafter reduced to 30 minutes (high drinkers), we further reduced the duration of the daily sessions to only 15 minutes (binge drinkers). We observed an increase in ethanol consumption (Figure 3) reaching about 1.2 g/kg and rats displayed clear signs of intoxication (i.e. sedation and ataxia: loss of locomotor coordination). The pattern of alcohol deliveries

and the number of lever presses observed in our models are presented in Figure 4. The pattern of alcohol deliveries of the BD rats clearly shows that these rats display a high rate of ethanol consumption.

After several weeks of chronic daily BD sessions, we also observed signs of withdrawal (e.g., aggressive behavior and vocalizations) and an increased motivation to consume alcohol even for a highly concentrated solution (30% ethanol). Finally, we also observed somatic damage in BD rats with these animals displaying typical signs of hepatic steatosis (Figure 5). In this model, we demonstrate that rats can consume very quickly, as is observed in human BD and as would be expected in a relevant animal model of BD.

3. Criteria for an animal model of BD

Here we propose seven criteria (see Table 1) that we believe need to be met for the behavior of BD in an animal model to correspond to that in humans and therefore, to serve as a valid model of human BD (Figure 6).

The first criterion is voluntary ethanol intake by oral ingestion. Numerous studies have shown that forced (passive) administration of addictive substances is not appropriate to decipher etiological factors involved in behavior compared with active administration. In addition, it is generally accepted that paradigms in which drug administration is contingent on an instrumental response (self-administration) are a better model for human addiction (Jacobs et al., 2003). Active self-administration behavior affects the nature and direction of drug-induced neuroplasticity (Jacobs et al., 2003) and may also involve an expectancy phenomenon (i.e., expecting to receive the drug is known to potentiate brain activation in humans) (Volkow et al., 2003). For example, studies on cocaine have demonstrated that active self-

administration has a greater effect on dopamine release compared with yoked or non-contingent delivery (Lecca et al., 2007, Wiskerke et al., 2016). Concerning ethanol, Gilpin et al. (Gilpin et al., 2012) have shown that voluntary (but not involuntary) BD during adolescence increases baseline drinking in adulthood in Wistar rats. Furthermore, oral ingestion clearly should be preferred to achieve face validity of the model and to mimic human drinking. In addition, food deprivation and sugar adulteration of the ethanol solution should be avoided because these manipulations may have an impact on motivation of the animal to consume ethanol and ethanol metabolism (Roberts et al., 1999), and can alter the dynamics of cue-ethanol memory reconsolidation (Puaud et al., 2018). Finally, as indicated above, the operant paradigm is preferred because it allows the study of other criteria that are central to the transition to dependence and some of its features, such as loss of control, compulsivity, high seeking (craving), motivation, loss of cognitive flexibility, behavioral sensitization and habit learning. This latter point is especially important since BD may be involved in the vulnerability to ethanol addiction (Gowin et al., 2017). Thus, it is crucial that addictive behaviors can be analyzed in the animal model of BD because, as in humans, it is possible that some binge drinkers may be categorized as dependent.

Second, sufficient levels of ethanol have to be consumed to achieve significant BEC and thus to induce visible signs of intoxication. Humans drinking ethanol in a BD pattern are seeking drunkenness and in some cases to ethylic coma. The 0.08g/dl threshold in the NIAAA definition of BD may also serve as a useful BEC threshold in animal models of BD since signs of intoxications are also visible in animals (even in outbred animals) that reach this BEC threshold after voluntary ethanol intake (Jeanblanc et al., 2018). A recent study in humans indicates that thresholds in

alcohol quantity (such as ≤56g (moderate drinkers), 70g+ (binge drinkers) and 140g+ (extreme binge drinkers) of ethanol per occasion are an important factor to consider since some cognitive abilities (e.g., acquisition of new verbal information) may be particularly affected, particularly in extreme binge drinkers (Nguyen-Louie et al., 2016).

Third, the drinking episode should be short and thus, animals should drink fast. We described here a study indicating that outbred rats can display signs of intoxication 15 minutes after the beginning of the drinking episode. Paradigms with drinking episodes of several hours may not demonstrate sufficient face validity because rodents metabolize ethanol more quickly compared with humans.

Fourth, drinking episodes should be both intermittent and repeated several days a week to model BD patterns as it may be observed in adolescent populations (Courtney and Polich, 2009). However, the pattern of BD may not correspond to everyday drinking as it is seen in ethanol dependent population (Rolland and Naassila, 2017). Thus, the fifth criterion specifies a few days without ethanol access should be included in the BD paradigm. Intermittent exposure to ethanol drinking is an important factor in the vulnerability to develop ethanol dependence (Kimbrough et al., 2017) and produce brain damage (Reynolds et al., 2015). The duration of episodic alcohol exposures should be from subchronic to chronic in the context of BD studies.

Since several studies in humans and animal models of BD have demonstrated both brain damage/cognitive deficits (Townshend and Duka, 2005, McQueeny et al., 2009) (Squeglia et al., 2014, Smith et al., 2015, Salas-Gomez et al., 2016, Cantacorps et al., 2017, Cohen-Gilbert et al., 2017, Molnar et al., 2018) and somatic

damage (Llerena et al., 2015, Mostofsky et al., 2015), the sixth criterion is that an animal model of BD should display this kind of damage (Ventura-Cots et al., 2017, Wegner et al., 2017). Studies in both humans and animals have shown that BD adversely affects both white and grey matter and that the neuro-inflammatory processes play an important role in ethanol-induced neurotoxicity (Jacobus and Tapert, 2013, Crews et al., 2016, Pascual et al., 2017a, Saba et al., 2017).

Finally, as stated above BD is a complex behavior and binge drinkers represent a heterogeneous population (Nguyen-Louie et al., 2016, Gierski et al., 2017). Thus, it is important to be able to study such an interindividual variability in an animal model of BD, which constitutes our seventh criterion.

4. Concluding remarks and need for future research

The choice of the animal species and the procedure of alcohol administration are crucial to create an appropriate animal model of BD for addressing both neurobiological and behavioral aspects. All the procedures discussed here have their advantages and their limitations. Each project and each scientific question need to be *a priori* challenged with the different models to ensure the most adequate choice. Animal models using forced/passive ethanol administration are largely used to explore brain and somatic consequences of BD. The other models using voluntary intake may display better face validity since they allow investigations of both the impact of the high speed of drinking and the motivational aspect of BD that may be useful to investigate the transition to alcohol dependence. Therefore, animal models of BD using voluntary intake should be preferred for future integrative and/or translational research especially because recent data indicate that this procedure can lead to very fast alcohol intake and induce both cognitive and liver damage. The

combination of rapid drinking with the ability to study the motivational aspects in the same animal model of BD may be the most important hallmarks of an appropriate model of human BD behavior. Indeed, in humans, the study of the motivation for BD is an important component in the field of research on BD. Few animal models of voluntary alcohol intoxication in rats are available, and most of the models have been developed with inbred mice leading to difficulties with the evaluation of an inter-individual vulnerability profile of BD. Important components of human BD behavior are the peer pressure and the social transmission. Social transmission of preference for ethanol has already been demonstrated in adolescent rats (Hunt et al., 2001). These aspects need to be investigated in future studies in order to continue to improve the face validity of the BD models. Producing voluntary BD in animals is now possible and opens new perspectives for research. Future research is also needed regarding several unexplored aspects of BD behavior such as the construct validity (brain circuits and cognitive functioning), predictive validity (efficacy of pharmacotherapies), the role of gender, the role of social interaction and individual determinants such as impulsivity and genetic variations.

Legends of the figures

Figure 1. Number of publications found on PubMed on BD. Number of publications for 'BD and mice", BD and rats" and "BD and students" per year.

Figure 2. BEC profiles in humans, rats and mice after alcohol administration using oral intake, gavage of intra-peritoneal injections. BEC profiles after ethanol administration as a single dose of 0.5 or 0.75 g/kg of a 20% ethanol solution in either by means of intra-gastric gavage or intra-peritoneal injections in mice or rats. In humans acute binge ethanol was given as 2 ml vodka 40% v/v ethanol/kg body weight in a total volume of 300 ml orange/strawberry juice. Adapted from Bala et al.; Walker & Ehlers and Rose et al. (Walker and Ehlers, 2009, Rose et al., 2013, Bala et al., 2014).

Figure 3. Limiting the duration of session promotes binge drinking in the operant paradigm. The cumulative number of lever presses are presented depending on the duration of the session 1h, 30min and 15min. Shorten the session duration increases very significantly the level of alcohol amount and the speed of drinking (from Jeanblanc and Naassila, unpublished data).

Figure 4. Pattern of alcohol deliveries in binge drinkers (14min access), high drinkers (30min access) and moderate drinkers (1h access). Each bar represents an alcohol delivery (0.1ml of 20% ethanol solution), the total number of lever presses is also indicated on the right. (from Jeanblanc and Naassila, unpublished data).

Figure 5. Hepatic gross morphology after BD. Representative liver harvested from the BD group (top picture) showed typical signs of steatosis, with more yellow and rough surfaces comparing with those of the alcohol naïve rats (bottom picture). (from Jeanblanc and Naassila, unpublished data).

Figure 6. Validity of the animal models of BD. Animal models of BD should display good face validity, construct validity and predictive validity.

References

Alaux-Cantin S, Warnault V, Legastelois R, Botia B, Pierrefiche O, Vilpoux C, Naassila M (2013) Alcohol intoxications during adolescence increase motivation for alcohol in adult rats and induce neuroadaptations in the nucleus accumbens. Neuropharmacology 67:521-531.

Anton M, Alen F, Gomez de Heras R, Serrano A, Pavon FJ, Leza JC, Garcia-Bueno B, Rodriguez de Fonseca F, Orio L (2017) Oleoylethanolamide prevents neuroimmune HMGB1/TLR4/NF-kB danger signaling in rat frontal cortex and depressive-like behavior induced by ethanol binge administration. Addict Biol 22:724-741.

Aufrere G, Le Bourhis B, Beauge F (1997) Ethanol intake after chronic intoxication by inhalation of ethanol vapour in rats: behavioural dependence. Alcohol 14:247-253.

Azarov AV, Woodward DJ (2014) Early ethanol and water intake: choice mechanism and total fluid regulation operate in parallel in male alcohol preferring (P) and both Wistar and Sprague Dawley rats. Physiol Behav 123:11-19.

Bala S, Marcos M, Gattu A, Catalano D, Szabo G (2014) Acute binge drinking increases serum endotoxin and bacterial DNA levels in healthy individuals. PLoS One 9:e96864.

Bell RL, Kimpel MW, McClintick JN, Strother WN, Carr LG, Liang T, Rodd ZA, Mayfield RD, Edenberg HJ, McBride WJ (2009) Gene expression changes in the nucleus accumbens of alcohol-preferring rats following chronic ethanol consumption. Pharmacol Biochem Behav 94:131-147.

Ben Hamida S, Neasta J, Lasek AW, Kharazia V, Zou M, Carnicella S, Janak PH, Ron D (2012) The small G protein H-Ras in the mesolimbic system is a molecular gateway to alcohol-seeking and excessive drinking behaviors. J Neurosci 32:15849-15858.

Bertola A, Mathews S, Ki SH, Wang H, Gao B (2013a) Mouse model of chronic and binge ethanol feeding (the NIAAA model). Nat Protoc 8:627-637.

Bertola A, Park O, Gao B (2013b) Chronic plus binge ethanol feeding synergistically induces neutrophil infiltration and liver injury in mice: a critical role for E-selectin. Hepatology 58:1814-1823.

Bito-Onon JJ, Simms JA, Chatterjee S, Holgate J, Bartlett SE (2011) Varenicline, a partial agonist at neuronal nicotinic acetylcholine receptors, reduces nicotine-induced increases in 20% ethanol operant self-administration in Sprague-Dawley rats. Addict Biol 16:440-449.

Blank SE, Duncan DA, Meadows GG (1991) Suppression of natural killer cell activity by ethanol consumption and food restriction. Alcohol Clin Exp Res 15:16-22.

Burnham NW, Thiele TE (2017) Voluntary Binge-like Ethanol Consumption Site-specifically Increases c-Fos Immunoexpression in Male C57BL6/J Mice. Neuroscience 367:159-168.

Cantacorps L, Alfonso-Loeches S, Moscoso-Castro M, Cuitavi J, Gracia-Rubio I, Lopez-Arnau R, Escubedo E, Guerri C, Valverde O (2017) Maternal alcohol binge drinking induces persistent neuroinflammation associated with myelin damage and behavioural dysfunctions in offspring mice. Neuropharmacology 123:368-384.

Carnicella S, Amamoto R, Ron D (2009) Excessive alcohol consumption is blocked by glial cell line-derived neurotrophic factor. Alcohol 43:35-43.

Carnicella S, Kharazia V, Jeanblanc J, Janak PH, Ron D (2008) GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse. Proc Natl Acad Sci U S A 105:8114-8119.
Carnicella S, Ron D, Barak S (2014) Intermittent ethanol access schedule in rats as a preclinical model of alcohol abuse. Alcohol 48:243-252.
Carnicella S, Yowell QV, Ron D (2011) Regulation of operant oral ethanol self-administration: a dose-response curve study in rats. Alcohol Clin Exp Res 35:116-125.
Carson EJ, Pruett SB (1996) Development and characterization of a binge drinking model in mice for evaluation of the immunological effects of ethanol. Alcohol Clin Exp Res 20:132-138.
Ceballos N, Babor TF (2017) Editor's Corner: Binge Drinking and the Evolving Language of Alcohol Research. J Stud Alcohol Drugs 78:488-490.
Chen MM, Palmer JL, Ippolito JA, Curtis BJ, Choudhry MA, Kovacs EJ (2013) Intoxication by intraperitoneal injection or oral gavage equally potentiates postburn organ damage and inflammation. Mediators Inflamm 2013:971481.
Chen P, Miyamoto Y, Mazagova M, Lee KC, Eckmann L, Schnabl B (2015) Microbiota Protects Mice Against Acute Alcohol-Induced Liver Injury. Alcohol Clin Exp Res 39:2313-2323.
Cippitelli A, Damadzic R, Singley E, Thorsell A, Ciccocioppo R, Eskay RL, Heilig M (2012) Pharmacological blockade of corticotropin-releasing hormone receptor 1 (CRH1R) reduces voluntary consumption of high alcohol concentrations in non-dependent Wistar rats. Pharmacol Biochem Behav 100:522-529.
Cohen-Gilbert JE, Nickerson LD, Sneider JT, Oot EN, Seraikas AM, Rohan ML, Silveri MM (2017) College Binge Drinking Associated with Decreased Frontal Activation to Negative Emotional Distractors during Inhibitory Control. Front Psychol 8:1650.
Colombo G, Maccioni P, Acciaro C, Lobina C, Loi B, Zaru A, Carai MA, Gessa GL (2014) Binge drinking in alcohol-preferring sP rats at the end of the nocturnal period. Alcohol 48:301-311.
Courtney KE, Polich J (2009) Binge drinking in young adults: Data, definitions, and determinants. Psychol Bull 135:142-156.
Crabbe JC, Harris RA, Koob GF (2011a) Preclinical studies of alcohol binge drinking. Ann N Y Acad Sci 1216:24-40.
Crabbe JC, Metten P, Rhodes JS, Yu CH, Brown LL, Phillips TJ, Finn DA (2009) A line of mice selected for high blood ethanol concentrations shows drinking in the dark to intoxication. Biol Psychiatry 65:662-670.
Crabbe JC, Ozburn AR, Metten P, Barkley-Levenson A, Schlumbohm JP, Spence SE, Hack WR, Huang LC (2017) High Drinking in the Dark (HDID) mice are sensitive to the effects of some clinically relevant drugs to reduce binge-like drinking. Pharmacol Biochem Behav 160:55-62.
Crabbe JC, Spence SE, Brown LL, Metten P (2011b) Alcohol preference drinking in a mouse line selectively bred for high drinking in the dark. Alcohol 45:427-440.
Crews FT, Vetreno RP, Broadwater MA, Robinson DL (2016) Adolescent Alcohol Exposure Persistently Impacts Adult Neurobiology and Behavior. Pharmacol Rev 68:1074-1109.
Cronise K, Finn DA, Metten P, Crabbe JC (2005) Scheduled access to ethanol results in motor impairment and tolerance in female C57BL/6J mice. Pharmacol Biochem Behav 81:943-953.

D'Souza El-Guindy NB, Kovacs EJ, De Witte P, Spies C, Littleton JM, de Villiers WJ, Lott AJ, Plackett TP, Lanzke N, Meadows GG (2010) Laboratory models available to study alcohol-induced organ damage and immune variations: choosing the appropriate model. Alcohol Clin Exp Res 34:1489-1511.

Darcq E, Morisot N, Phamluong K, Warnault V, Jeanblanc J, Longo FM, Massa SM, Ron D (2016) The Neurotrophic Factor Receptor p75 in the Rat Dorsolateral Striatum Drives Excessive Alcohol Drinking. J Neurosci 36:10116-10127.

Gierski F, Benzerouk F, De Wever E, Duka T, Kaladjian A, Quaglino V, Naassila M (2017) Cloninger's Temperament and Character Dimensions of Personality and Binge Drinking Among College Students. Alcohol Clin Exp Res 41:1970-1979.

Gilpin NW, Karanikas CA, Richardson HN (2012) Adolescent binge drinking leads to changes in alcohol drinking, anxiety, and amygdalar corticotropin releasing factor cells in adulthood in male rats. PLoS One 7:e31466.

Gowin JL, Sloan ME, Stangl BL, Vatsalya V, Ramchandani VA (2017) Vulnerability for Alcohol Use Disorder and Rate of Alcohol Consumption. Am J Psychiatry 174:1094-1101.

Griffin WC, 3rd, Lopez MF, Becker HC (2009) Intensity and duration of chronic ethanol exposure is critical for subsequent escalation of voluntary ethanol drinking in mice. Alcohol Clin Exp Res 33:1893-1900.

Hansen AW, Almeida FB, Bandiera S, Pulcinelli RR, Fragoso ALR, Schneider R, Jr., Barros HMT, Gomez R (2017) Taurine restores the exploratory behavior following alcohol withdrawal and decreases BDNF mRNA expression in the frontal cortex of chronic alcohol-treated rats. Pharmacol Biochem Behav 161:6-12.

Hermens DF, Lagopoulos J, Tobias-Webb J, De Regt T, Dore G, Juckes L, Latt N, Hickie IB (2013) Pathways to alcohol-induced brain impairment in young people: a review. Cortex 49:3-17.

Hingson RW, Zha W, White AM (2017) Drinking Beyond the Binge Threshold: Predictors, Consequences, and Changes in the U.S. Am J Prev Med 52:717-727.

Hopf FW, Chang SJ, Sparta DR, Bowers MS, Bonci A (2010) Motivation for alcohol becomes resistant to quinine adulteration after 3 to 4 months of intermittent alcohol self-administration. Alcohol Clin Exp Res 34:1565-1573.

Hwa LS, Chu A, Levinson SA, Kayyali TM, DeBold JF, Miczek KA (2011) Persistent escalation of alcohol drinking in C57BL/6J mice with intermittent access to 20% ethanol. Alcohol Clin Exp Res 35:1938-1947.

Jacobs EH, Smit AB, de Vries TJ, Schoffelmeer AN (2003) Neuroadaptive effects of active versus passive drug administration in addiction research. Trends Pharmacol Sci 24:566-573.

Jacobus J, Tapert SF (2013) Neurotoxic effects of alcohol in adolescence. Annu Rev Clin Psychol 9:703-721.

Jeanblanc J, He DY, Carnicella S, Kharazia V, Janak PH, Ron D (2009) Endogenous BDNF in the dorsolateral striatum gates alcohol drinking. J Neurosci 29:13494-13502.

Jeanblanc J, Lemoine S, Jeanblanc V, Alaux-Cantin S, Naassila M (2015) The Class I-Specific HDAC Inhibitor MS-275 Decreases Motivation to Consume Alcohol and Relapse in Heavy Drinking Rats. Int J Neuropsychopharmacol 18.

Jin L, Batra S, Jeyaseelan S (2017) Diminished neutrophil extracellular trap (NET) formation is a novel innate immune deficiency induced by acute ethanol

exposure in polymicrobial sepsis, which can be rescued by CXCL1. PLoS Pathog 13:e1006637.
Kamdar NK, Miller SA, Syed YM, Bhayana R, Gupta T, Rhodes JS (2007) Acute effects of naltrexone and GBR 12909 on ethanol drinking-in-the-dark in C57BL/6J mice. Psychopharmacology (Berl) 192:207-217.
Karelina K, Gaier KR, Prabhu M, Wenger V, Corrigan TE, Weil ZM (2017) Binge ethanol in adulthood exacerbates negative outcomes following juvenile traumatic brain injury. Brain Behav Immun 60:304-311.
Kaur S, Ryabinin AE (2010) Ghrelin receptor antagonism decreases alcohol consumption and activation of perioculomotor urocortin-containing neurons. Alcohol Clin Exp Res 34:1525-1534.
Kawashima K, Jerzy Glass GB (1975) Alcohol injury to gastric mucosa in mice and its potentiation by stress. Am J Dig Dis 20:162-172.
Kimbrough A, Kim S, Cole M, Brennan M, George O (2017) Intermittent Access to Ethanol Drinking Facilitates the Transition to Excessive Drinking After Chronic Intermittent Ethanol Vapor Exposure. Alcohol Clin Exp Res 41:1502-1509.
Kuntsche E, Kuntsche S, Thrul J, Gmel G (2017) Binge drinking: Health impact, prevalence, correlates and interventions. Psychol Health 32:976-1017.
Lannoy S, Billieux J, Poncin M, Maurage P (2017a) Binging at the campus: Motivations and impulsivity influence binge drinking profiles in university students. Psychiatry Res 250:146-154.
Lannoy S, D'Hondt F, Dormal V, Billieux J, Maurage P (2017b) Electrophysiological correlates of performance monitoring in binge drinking: Impaired error-related but preserved feedback processing. Clin Neurophysiol 128:2110-2121.
Le Bourhis B (1975) [Alcohol intoxication via the lung in rats]. C R Seances Soc Biol Fil 169:898-904.
Le Bourhis B, Aufrere G (1983) Pattern of alcohol administration and physical dependence. Alcohol Clin Exp Res 7:378-381.
Le Magnen J (1960) [Study of some factors associated with modifications of spontaneous ingestion of ethyl alcohol by the rat]. J Physiol (Paris) 52:873-884.
Lebourgeois S, Gonzalez-Marin MC, Jeanblanc J, Naassila M, Vilpoux C (2017) Effect of N-acetylcysteine on motivation, seeking and relapse to ethanol self-administration. Addict Biol.
Lecca D, Cacciapaglia F, Valentini V, Acquas E, Di Chiara G (2007) Differential neurochemical and behavioral adaptation to cocaine after response contingent and noncontingent exposure in the rat. Psychopharmacology (Berl) 191:653-667.
Lieber CS, DeCarli LM (1975) Alcoholic liver injury: experimental models in rats and baboons. Adv Exp Med Biol 59:379-393.
Liu L, Chen M, Zhao L, Zhao Q, Hu R, Zhu J, Yan R, Dai K (2017) Ethanol Induces Platelet Apoptosis. Alcohol Clin Exp Res 41:291-298.
Livy DJ, Parnell SE, West JR (2003) Blood ethanol concentration profiles: a comparison between rats and mice. Alcohol 29:165-171.
Llerena S, Arias-Loste MT, Puente A, Cabezas J, Crespo J, Fabrega E (2015) Binge drinking: Burden of liver disease and beyond. World J Hepatol 7:2703-2715.
McBride WJ, Kimpel MW, Schultz JA, McClintick JN, Edenberg HJ, Bell RL (2010) Changes in gene expression in regions of the extended amygdala of alcohol-preferring rats after binge-like alcohol drinking. Alcohol 44:171-183.

McBride WJ, Rodd ZA, Bell RL, Lumeng L, Li TK (2014) The alcohol-preferring (P) and high-alcohol-drinking (HAD) rats--animal models of alcoholism. Alcohol 48:209-215.
McQueeny T, Schweinsburg BC, Schweinsburg AD, Jacobus J, Bava S, Frank LR, Tapert SF (2009) Altered white matter integrity in adolescent binge drinkers. Alcohol Clin Exp Res 33:1278-1285.
Meyer EM, Long V, Fanselow MS, Spigelman I (2013) Stress increases voluntary alcohol intake, but does not alter established drinking habits in a rat model of posttraumatic stress disorder. Alcohol Clin Exp Res 37:566-574.
Mill DJ, Bito-Onon JJ, Simms JA, Li R, Bartlett SE (2013) Fischer rats consume 20% ethanol in a long-term intermittent-access two-bottle-choice paradigm. PLoS One 8:e79824.
Molnar SM, Beaton LE, Happer JP, Holcomb LA, Huang S, Arienzo D, Marinkovic K (2018) Behavioral and Brain Activity Indices of Cognitive Control Deficits in Binge Drinkers. Brain Sci 8.
Montesinos J, Pascual M, Rodriguez-Arias M, Minarro J, Guerri C (2016) Involvement of TLR4 in the long-term epigenetic changes, rewarding and anxiety effects induced by intermittent ethanol treatment in adolescence. Brain Behav Immun 53:159-171.
Morris LS, Dowell NG, Cercignani M, Harrison NA, Voon V (2018) Binge drinking differentially affects cortical and subcortical microstructure. Addict Biol 23:403-411.
Mostofsky E, van der Bom JG, Mukamal KJ, Maclure M, Tofler GH, Muller JE, Mittleman MA (2015) Risk of myocardial infarction immediately after alcohol consumption. Epidemiology 26:143-150.
Neasta J, Ben Hamida S, Yowell Q, Carnicella S, Ron D (2010) Role for mammalian target of rapamycin complex 1 signaling in neuroadaptations underlying alcohol-related disorders. Proc Natl Acad Sci U S A 107:20093-20098.
Nguyen-Louie TT, Tracas A, Squeglia LM, Matt GE, Eberson-Shumate S, Tapert SF (2016) Learning and Memory in Adolescent Moderate, Binge, and Extreme-Binge Drinkers. Alcohol Clin Exp Res 40:1895-1904.
Pascual M, Balino P, Aragon CM, Guerri C (2015) Cytokines and chemokines as biomarkers of ethanol-induced neuroinflammation and anxiety-related behavior: role of TLR4 and TLR2. Neuropharmacology 89:352-359.
Pascual M, Blanco AM, Cauli O, Minarro J, Guerri C (2007) Intermittent ethanol exposure induces inflammatory brain damage and causes long-term behavioural alterations in adolescent rats. Eur J Neurosci 25:541-550.
Pascual M, Do Couto BR, Alfonso-Loeches S, Aguilar MA, Rodriguez-Arias M, Guerri C (2012) Changes in histone acetylation in the prefrontal cortex of ethanol-exposed adolescent rats are associated with ethanol-induced place conditioning. Neuropharmacology 62:2309-2319.
Pascual M, Montesinos J, Guerri C (2017a) Role of the innate immune system in the neuropathological consequences induced by adolescent binge drinking. J Neurosci Res.
Pascual M, Montesinos J, Marcos M, Torres JL, Costa-Alba P, Garcia-Garcia F, Laso FJ, Guerri C (2017b) Gender differences in the inflammatory cytokine and chemokine profiles induced by binge ethanol drinking in adolescence. Addict Biol 22:1829-1841.
Reynolds AR, Berry JN, Sharrett-Field L, Prendergast MA (2015) Ethanol withdrawal is required to produce persisting N-methyl-D-aspartate receptor-dependent

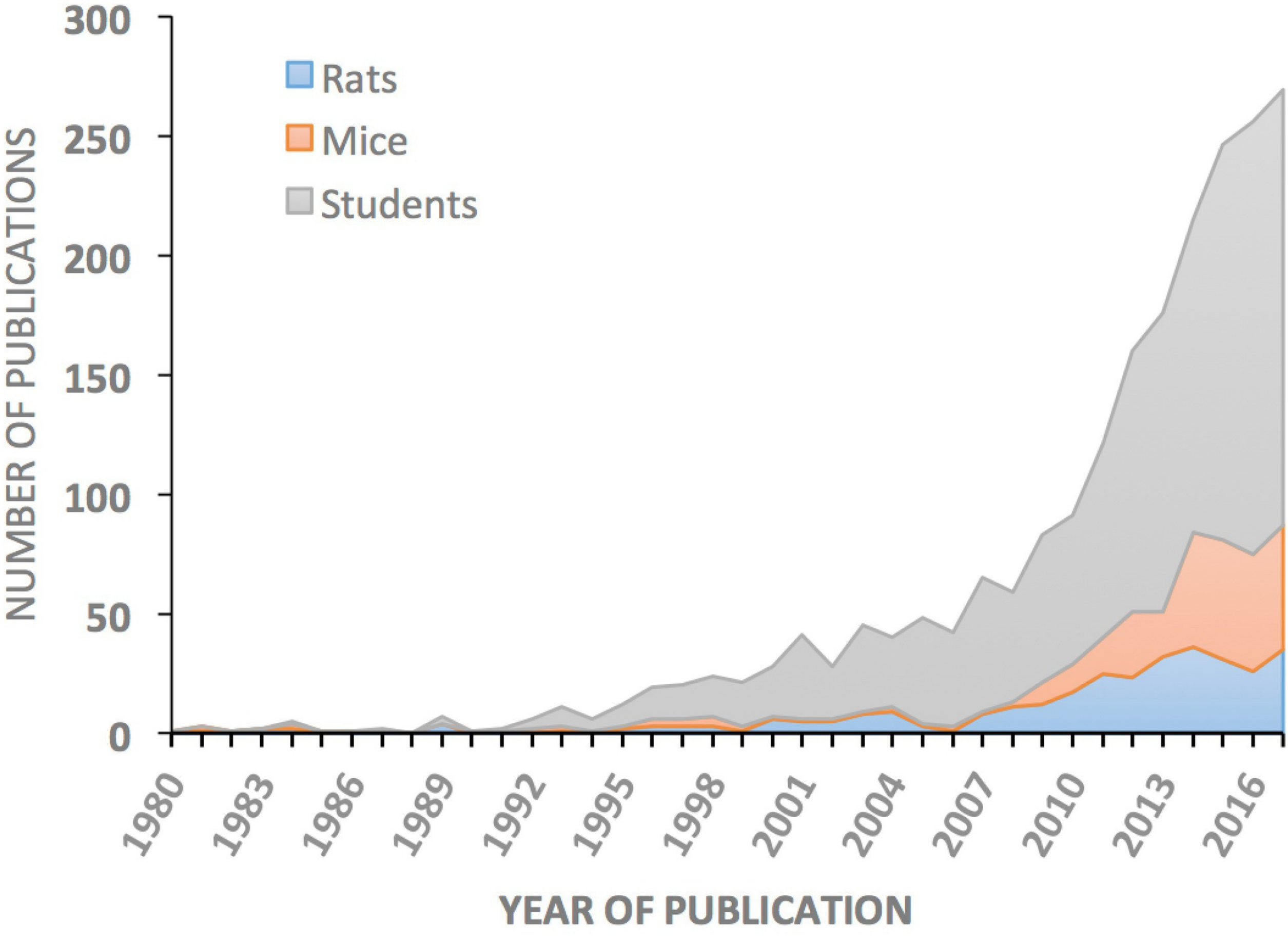
hippocampal cytotoxicity during chronic intermittent ethanol exposure. Alcohol 49:219-227.
Rhodes JS, Best K, Belknap JK, Finn DA, Crabbe JC (2005) Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. Physiol Behav 84:53-63.
Rhodes JS, Ford MM, Yu CH, Brown LL, Finn DA, Garland T, Jr., Crabbe JC (2007) Mouse inbred strain differences in ethanol drinking to intoxication. Genes Brain Behav 6:1-18.
Roberts AJ, Heyser CJ, Koob GF (1999) Operant self-administration of sweetened versus unsweetened ethanol: effects on blood alcohol levels. Alcohol Clin Exp Res 23:1151-1157.
Roine RP, Gentry RT, Lim RT, Jr., Baraona E, Lieber CS (1991) Effect of concentration of ingested ethanol on blood alcohol levels. Alcohol Clin Exp Res 15:734-738.
Rolland B, Chazeron I, Carpentier F, Moustafa F, Viallon A, Jacob X, Lesage P, Ragonnet D, Genty A, Geneste J, Poulet E, Dematteis M, Llorca PM, Naassila M, Brousse G (2017) Comparison between the WHO and NIAAA criteria for binge drinking on drinking features and alcohol-related aftermaths: Results from a cross-sectional study among eight emergency wards in France. Drug Alcohol Depend 175:92-98.
Rolland B, Naassila M (2017) Binge Drinking: Current Diagnostic and Therapeutic Issues. CNS Drugs 31:181-186.
Rose JH, Calipari ES, Mathews TA, Jones SR (2013) Greater ethanol-induced locomotor activation in DBA/2J versus C57BL/6J mice is not predicted by presynaptic striatal dopamine dynamics. PLoS One 8:e83852.
Saba W, Goutal S, Auvity S, Kuhnast B, Coulon C, Kouyoumdjian V, Buvat I, Leroy C, Tournier N (2017) Imaging the neuroimmune response to alcohol exposure in adolescent baboons: a TSPO PET study using (18) F-DPA-714. Addict Biol.
Sabino V, Kwak J, Rice KC, Cottone P (2013) Pharmacological characterization of the 20% alcohol intermittent access model in Sardinian alcohol-preferring rats: a model of binge-like drinking. Alcohol Clin Exp Res 37:635-643.
Salas-Gomez D, Fernandez-Gorgojo M, Pozueta A, Diaz-Ceballos I, Lamarain M, Perez C, Sanchez-Juan P (2016) Binge Drinking in Young University Students Is Associated with Alterations in Executive Functions Related to Their Starting Age. PLoS One 11:e0166834.
Schulteis G, Markou A, Cole M, Koob GF (1995) Decreased brain reward produced by ethanol withdrawal. Proc Natl Acad Sci U S A 92:5880-5884.
Silvestre de Ferron B, Bennouar KE, Kervern M, Alaux-Cantin S, Robert A, Rabiant K, Antol J, Naassila M, Pierrefiche O (2015) Two Binges of Ethanol a Day Keep the Memory Away in Adolescent Rats: Key Role for GLUN2B Subunit. Int J Neuropsychopharmacol 19.
Simms JA, Steensland P, Medina B, Abernathy KE, Chandler LJ, Wise R, Bartlett SE (2008) Intermittent access to 20% ethanol induces high ethanol consumption in Long-Evans and Wistar rats. Alcohol Clin Exp Res 32:1816-1823.
Simon-O'Brien E, Alaux-Cantin S, Warnault V, Buttolo R, Naassila M, Vilpoux C (2015) The histone deacetylase inhibitor sodium butyrate decreases excessive ethanol intake in dependent animals. Addict Biol 20:676-689.
Smith CC, Guevremont D, Williams JM, Napper RM (2015) Apoptotic cell death and temporal expression of apoptotic proteins Bcl-2 and Bax in the hippocampus,

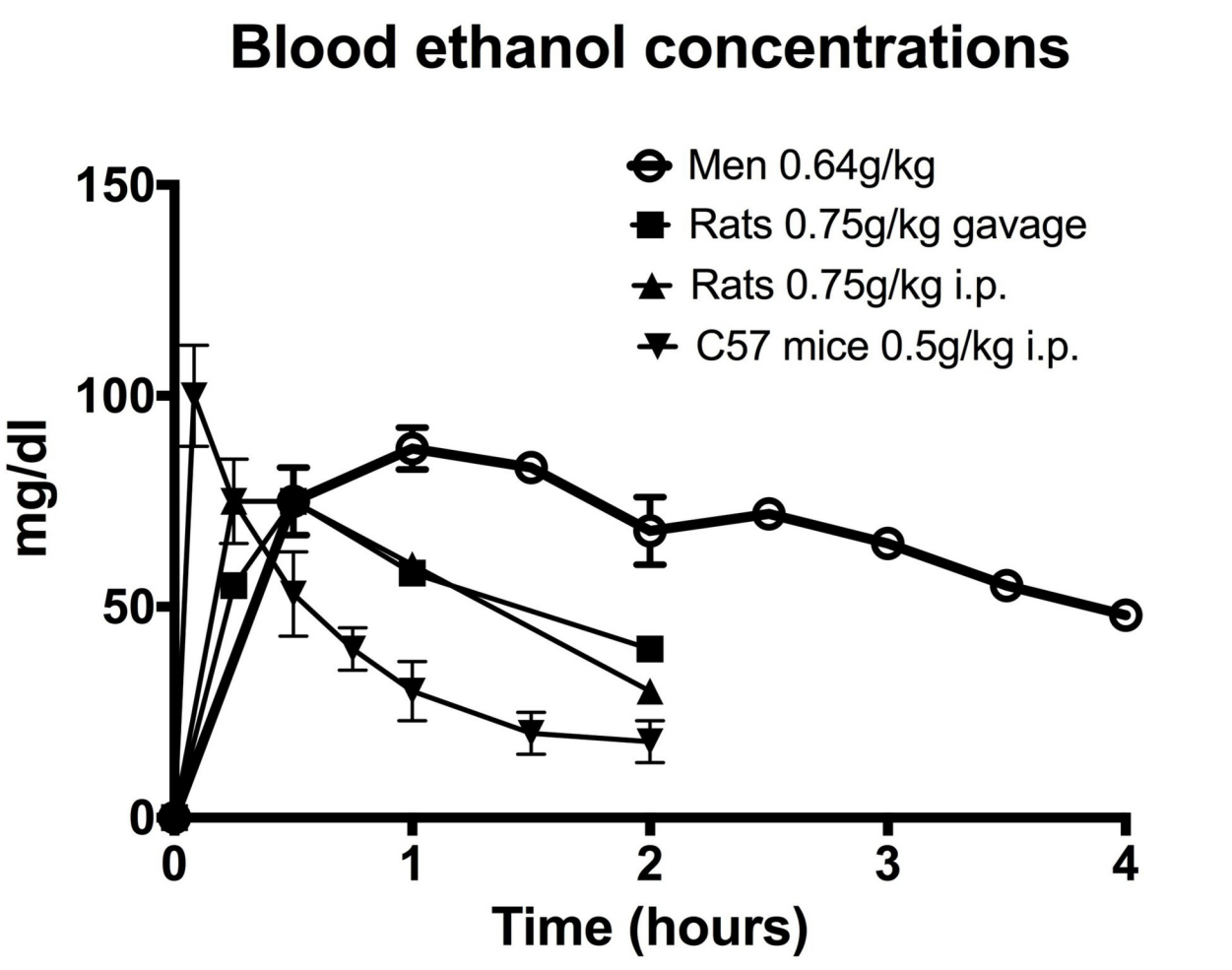
following binge ethanol in the neonatal rat model. Alcohol Clin Exp Res 39:36-44.
Smith KW, Gierski F, Andre J, Dowell NG, Cercignani M, Naassila M, Duka T (2017) Altered white matter integrity in whole brain and segments of corpus callosum, in young social drinkers with binge drinking pattern. Addict Biol 22:490-501.
Spoelder M, Flores Dourojeanni JP, de Git KCG, Baars AM, Lesscher HMB, Vanderschuren L (2017a) Individual differences in voluntary alcohol intake in rats: relationship with impulsivity, decision making and Pavlovian conditioned approach. Psychopharmacology (Berl) 234:2177-2196.
Spoelder M, Pol S, Janssen BSG, Baars AM, Vanderschuren L, Lesscher HMB (2017b) Loss of control over alcohol seeking in rats depends on individual vulnerability and duration of alcohol consumption experience. Behav Pharmacol 28:334-344.
Squeglia LM, Jacobus J, Tapert SF (2014) The effect of alcohol use on human adolescent brain structures and systems. Handb Clin Neurol 125:501-510.
Steensland P, Simms JA, Holgate J, Richards JK, Bartlett SE (2007) Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. Proc Natl Acad Sci U S A 104:12518-12523.
Thiele TE, Crabbe JC, Boehm SL, 2nd (2014) "Drinking in the Dark" (DID): a simple mouse model of binge-like alcohol intake. Curr Protoc Neurosci 68:9 49 41-12.
Thombs DL, Dodd V, Pokorny SB, Omli MR, O'Mara R, Webb MC, Lacaci DM, Werch C (2008) Drink specials and the intoxication levels of patrons exiting college bars. Am J Health Behav 32:411-419.
Thompson KJ, Nazari SS, Jacobs WC, Grahame NJ, McKillop IH (2017) Use of a crossed high alcohol preferring (cHAP) mouse model with the NIAAA-model of chronic-binge ethanol intake to study liver injury. Alcohol Alcohol 52:629-637.
Townshend JM, Duka T (2002) Patterns of alcohol drinking in a population of young social drinkers: a comparison of questionnaire and diary measures. Alcohol Alcohol 37:187-192.
Townshend JM, Duka T (2005) Binge drinking, cognitive performance and mood in a population of young social drinkers. Alcohol Clin Exp Res 29:317-325.
Ventura-Cots M, Watts AE, Bataller R (2017) Binge drinking as a risk factor for advanced alcoholic liver disease. Liver Int 37:1281-1283.
Volkow ND, Wang GJ, Ma Y, Fowler JS, Zhu W, Maynard L, Telang F, Vaska P, Ding YS, Wong C, Swanson JM (2003) Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. J Neurosci 23:11461-11468.
Walker BM, Ehlers CL (2009) Age-related differences in the blood alcohol levels of Wistar rats. Pharmacol Biochem Behav 91:560-565.
Wang W, Xu MJ, Cai Y, Zhou Z, Cao H, Mukhopadhyay P, Pacher P, Zheng S, Gonzalez FJ, Gao B (2017) Inflammation is independent of steatosis in a murine model of steatohepatitis. Hepatology 66:108-123.
Wegner SA, Pollard KA, Kharazia V, Darevsky D, Perez L, Roychowdhury S, Xu A, Ron D, Nagy LE, Hopf FW (2017) Limited Excessive Voluntary Alcohol Drinking Leads to Liver Dysfunction in Mice. Alcohol Clin Exp Res 41:345-358.
Weiss F, Parsons LH, Schulteis G, Hyytia P, Lorang MT, Bloom FE, Koob GF (1996) Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. J Neurosci 16:3474-3485.

Wilcox MV, Cuzon Carlson VC, Sherazee N, Sprow GM, Bock R, Thiele TE, Lovinger DM, Alvarez VA (2014) Repeated binge-like ethanol drinking alters ethanol drinking patterns and depresses striatal GABAergic transmission. Neuropsychopharmacology 39:579-594.
Wise RA (1973) Voluntary ethanol intake in rats following exposure to ethanol on various schedules. Psychopharmacologia 29:203-210.
Wiskerke J, Schoffelmeer AN, De Vries TJ (2016) Response contingency directs long-term cocaine-induced neuroplasticity in prefrontal and striatal dopamine terminals. Eur Neuropsychopharmacol 26:1667-1672.
Yang L, Long C, Faingold CL (2001) Neurons in the deep layers of superior colliculus are a requisite component of the neuronal network for seizures during ethanol withdrawal. Brain Res 920:134-141.
Yao YL, Han X, Li ZM, Lian LH, Nan JX, Wu YL (2017) Acanthoic Acid Can Partially Prevent Alcohol Exposure-Induced Liver Lipid Deposition and Inflammation. Front Pharmacol 8:134.

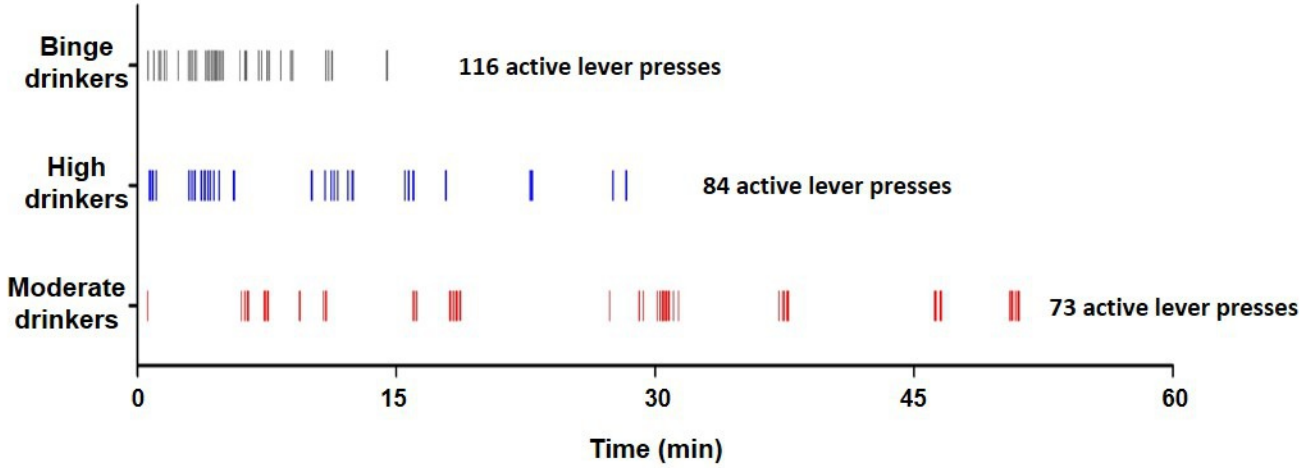
Acknowledgements

BR & MN received a grant from the “Fonds Actions-Addictions” (http://actions-addictions.org), which is an independent French foundation supporting evidenced-based actions against addictive disorders. MM received an invited-professor grant from the University of Picardie Jules Verne.


300
250
200
150
100
50
0
NUMBER OF PUBLICATIONS
Rats
Mice
Students
1980
1983
1986
1989
1992
1995
1998
2001
2004
2007
2010
2013
2016
YEAR OF PUBLICATION


Blood ethanol concentrations
Men 0.64g/kg
Rats 0.75g/kg gavage
Rats 0.75g/kg i.p.
C57 mice 0.5g/kg i.p.
150
100
50
0
mg/dl
0
1
2
3
4
Time (hours)

Ethanol Consumed
(g/kg)
1
0.5
0.25
FR3 – 20% Ethanol
15 minutes
FR3 – 20% Ethanol
30 minutes
FR3 – 10% Ethanol
1 hour
15’
30’
1 hr
Durations of the sessions


Binge drinkers
116 active lever presses
High drinkers
84 active lever presses
Moderate drinkers
73 active lever presses
0
15
30
45
60
Time (min)

Cognitive impairments

Construct validity

Decision making

Brain & somatic damages

Impulsivity

Brain circuits

Neuro-inflammation

Pharmaco-therapies

Speed of drinking

Face validity

Predictive validity

Signs of intoxication

Addiction-vulnerability

Social interaction/ transmission

Drunkenness hangover

Frequency Pattern of Drinking

Table 1.

Title: Criteria for an animal model of BD.

Criteria for an animal model of BD
1- Voluntary intake / oral ingestion (without food deprivation or sweetener adulteration)
2- Quantity (>0.08g/dl) / visible signs of behavioral intoxication
3- Fast intake
4- Duration (repeated and at least subchronic)
5- Frequency / intermittence (few days off)
6- Brain damage/cognitive deficits and somatic damage (such as on liver)
7- Large inter-individual variability and possibility to investigate transition to dependence