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INFLUENCE OF SOCIAL STRESS IN THE REWARDING EFFECTS OF MDMA AND ALCOHOL

DOCTORAL THESIS

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La Dra. Maria Asunción Aguilar Calpe, Profesora Titular de Psicobiología de la Unidad de Investigación Psicobiología de las Drogodependencias, del Departamento de Psicobiología de la Universitat de Valencia,

CERTIFICA

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Fdo. Maria A. Aguilar.

A mis padres y hermanas por confiar siempre en mí.

A Antonio, simplemente por TODO.

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ABBREVIATIONS

2,5-dimethoxy-4-bromoamphetamine (DOB)

2,5-dimethoxy-4-methylamphetamine (DOM)

3,4 methylenedioxymethylamphetamine (MDMA)

5-hydroxyindolacetic acid (5-HIAA)

6-cyano-7-nitroquinoxaline-2,3-dione (CNQX)

7-nitroindazole (7-NI)

Adrenocorticotropin hormone (ACTH)

Anterior cingulate cortex (ACC)

Bed nucleus of stria terminalis (BNST)

Brain-derived neurotrophic factor (BDNF)

Cannabinoid receptor 1 (CB1)

Central nervous system (SNC)

Conditioned place preference (CPP)

Conditioned stimuli (CSs)

Corticotropin-releasing factor (CRF)

Cyclooxygenase-2 (COX-2)

Deoxyribonucleic acid (DNA)

Dopamine (DA)

Dopamine regulated phosphoprotein-32 (DARPP-32)

Drug Enforcement Administration (DEA)

Elevated plus maze (EPM)

Encuesta Domiciliaria sobre Alcohol y Drogas en España (EDADES)

Encuesta Estatal sobre el Uso de Drogas en Enseñanzas Secundarias (ESTUDES)

Ethanol (EtOH)

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

Extracellular signal-regulated kinase (ERK)

Fixed interval (FI)

Fixed ratio (FR)

Food and Drug Administration (FDA)

Gamma-aminobutyric acid (GABA)

Government Delegation for the National Plan on Drugs (DGPNSD)

High performance liquid chromatography (HPLC)

Histone deacetylases (HDAC)

Hypothalamus-pituitary-adrenal (HPA)

Inducible NO synthase (iNOS)

Instituto Nacional de Toxicología (INT)

kappa opioid receptors (KORs)

Medial PFC (mPFC)

Memantine (MEM)

Messenger ribonucleic acid (mRNA)

Methylene-dioxy-methamphetamine (MDM)

DNA Methyltransferases (DNMT)

Nitric oxide (NO)

Nitric oxide synthase (NOS)

N-methyl-D-aspartic acid (NMDA)

Noradrenaline (NA)

Nucleus accumbens (NAcc)

Orbitofrontal cortex (OFC)

p38 mitogen-activated protein kinase (MAPK)

Positron emission tomography (PET)

Post natal day (PND)

Prefrontal cortex (PFC)

Proopiomelanocortin (POMC)

Repeated social defeat (RSD)

Self-administration (SA)

Serotonin transporters (SERT)

Serotonine (5-HT)

Shell of the NAcc (NAccsh)

Single photon emission computed tomography (SPECT)

United Nations Office on Drugs and Crime (UNODC)

Ventral Palid (VP)

Ventral tegmental area (VTA)

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)

RESUMEN

La adicción a las drogas es un importante problema en nuestra sociedad con graves consecuencias jurídicas, médicas y sociales para los consumidores. Se trata de un trastorno caracterizado por la pérdida de control sobre el uso de la droga, su búsqueda compulsiva y la aparición de un estado emocional negativo en ausencia de la misma. Por su categoría legal, existen dos amplios tipos de sustancias de abuso, legales e ilegales. El alcohol es la droga legal más consumida tanto por adultos como por adolescentes. Por otra parte, entre las sustancias ilegales, los datos epidemiológicos apuntan que el éxtasis o MDMA es una sustancia ampliamente consumida entre los adolescentes y adultos jóvenes sobre todo en fiestas "rave" donde los consumidores pasan horas, incluso días, haciendo uso de esta sustancia. La adolescencia constituye un periodo de alta vulnerabilidad debido a la inmadurez cerebral, siendo muy perjudicial en esta fase de la vida el consumo de drogas y la exposición a situaciones ambientales negativas. En concreto, se ha demostrado que el estrés social puede provocar el inicio, escalada y la reinstauración en el consumo de drogas en modelos animales. Por ello, el objetivo del presente trabajo ha sido estudiar el efecto del estrés social agudo y repetido sobre las propiedades reforzantes de MDMA (1.25 y 10 mg/kg) y alcohol (1.25 y 2.5 g/kg) en ratones macho adolescentes y adultos jóvenes. Para ello se ha utilizado tres paradigmas principales, la derrota social, el condicionamiento de lugar y el procedimiento de "two-bottle choice". Para inducir estrés social los animales fueron sometidos a dos tipos de derrota social en un encuentro agonístico con un animal coespecífico agresivo. En la derrota social aguda los ratones experimentales son expuestos a un encuentro agonístico con otro ratón macho en un área neutral inmediatamente antes de la exposición a la droga (cuatro sesiones separadas 48 horas). En la derrota social repetida los ratones experimentales son expuestos a un encuentro agonístico en la jaula del oponente (modelo residente-intruso) de forma repetida e intermitente (cuatro sesiones separadas 72 horas) tres semanas antes de la exposición a la droga. Se realizó una medición de los niveles de corticosterona

en sangre tras la primera y cuarta derrota en los dos modelos de estrés social. En el condicionamiento de lugar se utiliza una caja con dos compartimentos claramente diferenciados en función del color y de la textura del suelo. Para la adquisición del condicionamiento, tras la administración de la droga el animal es confinado en uno de los compartimentos, por tanto, es un modelo de los efectos reforzantes o aversivos condicionados de las drogas. Tras la adquisición del condicionamiento se puede evaluar también su extinción y su reinstauración por la re-exposición a la droga ("priming"). En el procedimiento de "two-bottle choice" el animal tiene acceso a dos botellas, una con agua y otra con alcohol, en su propia jaula. Por tanto, es un modelo del consumo voluntario de alcohol. Asimismo también hemos evaluado el efecto del estrés social sobre otras conductas o procesos como la ansiedad (en el laberinto elevado en cruz), depresión (en el "tail-suspension test"), interacción social, aprendizaje (reconocimiento de objeto, "Hebb-Williams maze") y memoria (evitación pasiva). A su vez, hemos estudiado la base neurobiológica que subyace a los efectos reforzantes de la MDMA y su modulación por el estrés, evaluando el papel del sistema glutamatérgico y de la vía del óxido nítrico. Por otra parte, dado que el alcohol es la principal sustancia adictiva consumida a nivel mundial, y que la finalidad ultima del trabajo es avanzar en el conocimiento de los mecanismos neurobiológicos que subyacen a la adicción, hemos estudiado el papel de los receptores opioides mu en la ingesta de alcohol en el paradigma de "two-bottle choice". Los ratones adultos jóvenes adquieren un condicionamiento de preferencia de lugar (CPL) tras el condicionamiento con 1.25 y 10 mg/kg de MDMA. Este efecto reforzante del MDMA es bloqueado por la exposición a derrota social aguda. Por su parte los ratones adolescentes sólo muestran CPL tras el condicionamiento con 10 mg/kg de MDMA y la derrota social aguda no modifica este efecto. Además la derrota aguda induce una menor respuesta de estrés en adolescentes que en adultos jóvenes, ya que los niveles de corticosterona sólo aumentan inmediatamente después de la derrota social en ratones adultos jóvenes. Estos resultados indican que los ratones

adultos jóvenes son más sensitivos a los efectos reforzantes del MDMA y que el estrés inducido por la derrota social en adultos jóvenes interfiere con la adquisición del CPL. Por el contrario, los ratones adolescentes y adultos jóvenes expuestos a derrota social repetida (DSR) muestran un aumento a largo plazo en su sensibilidad a los efectos reforzantes del MDMA. Tres semanas después de la exposición a DSR se observó un incremento en la duración del CPL inducido por 1.25 y 10 mg/kg de MDMA en ratones adolescentes y adultos jóvenes. Asimismo se observó un aumento de la vulnerabilidad a la reinstauración inducida por priming en ratones expuestos a DSR durante la adolescencia y condicionados tres semanas después con 1.25 mg/kg de MDMA. El incremento en los efectos reforzantes y reinstauradores del MDMA en ratones expuestos a DSR durante la adolescencia es observado a pesar de que esos ratones muestran niveles más bajos de corticosterona que los ratones adultos, indicando la elevada vulnerabilidad del cerebro adolescente a los efectos de la exposición al estrés. Con respecto al papel del sistema glutamatérgico en los efectos reforzantes condicionados del éxtasis, hemos visto que estos efectos dependen de la activación de los receptores glutamatérgicos NMDA ya que el antagonista NMDA memantina inhibe la adquisición del CPL inducido por éxtasis y bloquea la reinstauración inducida por la re-exposición a una dosis "priming" de MDMA. Asimismo, con respecto a la influencia del sistema opioide en los efectos reforzantes del alcohol, hemos observado que la administración del antagonista opioide mu GSK1521498 (0.1, 1 y 3 mg/kg) reduce el consumo de alcohol en el paradigma de "two-bottle choice" en ratas con preferencia por el alcohol, lo que sugiere la utilidad de este compuesto para el tratamiento del alcoholismo. Nuestros resultados también han demostrado que la combinación de MDMA (10 mg/kg) con la derrota social aguda induce déficits cognitivos tales como una inhibición de la memoria implícita (evitación pasiva) y un deterioro de la memoria de reconocimiento (test de reconocimiento de objeto), así como un incremento de la inmovilidad en el "tail suspension test" que es un modelo animal de depresión, y una

respuesta motora reducida al “priming” con MDMA. Con respecto al alcohol, la derrota social aguda y repetida revierte la aversión condicionada a un lugar inducida por la dosis alta de alcohol (2.5 g/kg) e incrementa el consumo voluntario de esta sustancia en el paradigma de “two-bottle choice” en ratones, lo que sugiere que el estrés social aumenta los efectos reforzantes del alcohol. Con respecto al papel de otros receptores glutamatérgicos en los efectos reforzantes del éxtasis y en la influencia que ejerce el estrés social sobre dichos efectos, hemos demostrado que los receptores NMDA, AMPA y la vía del óxido nítrico están implicadas en los efectos reforzantes condicionados del éxtasis. La administración del antagonista NMDA memantina (10 mg/kg), del antagonista AMPA CNQX (0.25, 1 y 5 mg/kg) y del inhibidor de la síntesis de óxido nítrico 7-nitroindazole (7.25 y 12.5 mg/kg) bloquean la adquisición del CPL inducido por éxtasis en ratones. Asimismo, la administración de memantine (5 mg/kg) y de 7-nitroindazole (7.25 mg/kg) revierte los efectos deteriorantes de la derrota social aguda sobre el CPL inducido por éxtasis, lo que sugiere que el sistema glutamatérgico y la vía del óxido nítrico están implicados en estos efectos del estrés social.

En conjunto estos resultados indican que la exposición al estrés social (tanto agudo como a largo plazo) incrementa los efectos reforzantes de MDMA y alcohol y produce diferentes alteraciones conductuales, por ejemplo una reducción de la conducta social, que pueden estar relacionadas con el incremento en el consumo. Los antagonistas glutamatérgicos y la inhibición de la síntesis de óxido nítrico bloquean los efectos reforzantes de la MDMA y el antagonismo de los receptores opiáceos mu disminuye la búsqueda y consumo de alcohol. El avance en el conocimiento de los sistemas de neurotransmisión implicados en los efectos reforzantes de la MDMA y el alcohol puede contribuir al desarrollo de estrategias farmacológicas para el tratamiento de la adicción a la estas drogas.

Palabras clave: MDMA, Ethanol, Derrota social, alteraciones conductuales, CPL, “two-bottle choice”, ratón, rata, adolescencia

ABSTRACT

Drug addiction is a serious problem in our society and has serious legal, medical and social consequences for consumers. This disorder is characterised by an impaired control over substance use, compulsive drug seeking, and the emergence of a negative emotional state in the absence of the drug. With regard to legality, there are two broad types of substances of abuse: legal and illegal. Alcohol is the most consumed legal substance by adults and adolescents. Among illegal substances, epidemiologic data suggest that *ecstasy*, or MDMA, is a widely used substance among adolescents and young adults, especially in "raves", where consumers spend hours, even days, using this substance. Adolescence is a period of enhanced vulnerability due to the lack of brain maturation, and consumption of drugs of abuse and exposure to different negative environmental conditions is especially harmful at this stage of life. It has been demonstrated that social stress can trigger onset, escalation and reinstatement of drug use in animal models. Therefore, the objective of this work was to study the effects of acute and repeated social stress on the rewarding properties of alcohol and MDMA using the place preference paradigm (CPP) and the two-bottle choice procedure. In addition, we set out to evaluate the effects of social stress on several behaviours or processes (anxiety, depression, social interaction, learning and memory). We have also studied the neurobiological aspects underlying the rewarding effects of MDMA and their modulation by stress, assessing along the way the role of the glutamatergic system and nitric oxide (NO) pathway. Moreover, since alcohol is the main addictive substance consumed in the world, we have studied the role of the opioid system in the rewarding effects and intake of ethanol. Overall, our results indicate that exposure to social stress (both acute and long-term) increases the rewarding effects of MDMA and ethanol and induces different behavioural alterations, such as a reduction of social interaction, which is related with an increase in drug consumption. Glutamate antagonists and inhibition of NO synthesis block the rewarding effects of MDMA and

antagonism of mu opioid receptors decreases alcohol seeking and intake. Advances in knowledge of the neurotransmitter systems implicated in the rewarding effects of MDMA and alcohol are likely to contribute to the development of pharmacological strategies for the treatment of drug addiction.

Key word: MDMA, Ethanol, Social Defeat, Behavioural alterations, CPP, two-bottle choice, mice, rat, adolescence,

1.- GENERAL INTRODUCTION

1.- GENERAL INTRODUCTION

Drug addiction can be defined as a chronic, relapsing disorder that has been characterised by a compulsion to seek and take drugs, loss of control over drug intake, and emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome when access to the drug is prevented (Koob, 2013). In this sense, it is a chronic and recurrent illness characterised by a relapse to drug comsumption even after long-term periods of abstinence (Koob, 2010; Koob & Volkow, 2010). Moreover, it is well known that environmental factors can influence the addictive disorders (Ellenbroek et al., 2005; Enoch, 2006). Exposure to stressful events can render people more prone to abusing addictive substances (Sinha, 2001; Koob & Kreek, 2007; Miczek et al., 2008) and there is a positive association between stress and increased drug intake and / or relapse to drug use (Cruz et al., 2011; Boyson et al., 2014; Burke & Miczek, 2014; Fox et al., 2015) in humans and animal models. Using the self-administration (SA) and the conditioned place preference (CPP) paradigms, it has been demonstrated that stress enhances acquisition and reinstatement of drug seeking (Rodríguez-Arias et al., 2013; Aguilar et al., 2013).

Although there are differents types of stressors such as pharmacological, physical, emotional or social, the last ones (often studied in the form of social defeat, subordination stress, maternal separation and social isolation) may represent types of stressors with ecological and ethological validity, since in humans, emotional stressors

are primarily activators of stress response. In this work we induced the stress response by the exposure to different forms of social defeat, an important factor that may lead to psychopathological changes and disorders (Björkqvist, 2001; Miczek et al., 2008; Garcia-Pardo et al., 2014). In rodents, after being defeated, profound pshysiological and behavioral changes were observed (de Groot et al., 1999; Lumley et al., 1999; Keeney et al., 2001; Griebel et al., 2002). It has been shown several times that exposure to different procedures of social defeat increases the rewarding and reinstating effects of different types of drugs chiefly psychostimulant drugs, such as cocaine and amphetamine, in the self- administration and conditioned place preference (CPP) paradigms (Miczek et al., 2008; Neisewander et al., 2012; Aguilar et al., 2013).

Data from human and animal studies confirm that *ecstasy*, or MDMA (3,4 methylenedioxymethylamphetamine), is a drug of abuse with addictive potential (Daza-Losada et al., 2007; Davis & Rosenberg, 2014). MDMA abuse has been documented as a result of chronic consumption (Cottler et al., 2001; Leung et al., 2010), and some *ecstasy* users admit becoming concerned about their use (Degenhardt et al., 2010; Roger-Sanchez et al., 2013b). The typical recreational use of MDMA is often characterized by a pattern of repeated frequent administrations during a short period of time, also known as a binge administration (Badon et al., 2002) in night parties, raves or discos, with short-term effects after consumption such as hyperactivity, mental perspicacity and reduced fatigue (Nichols, 1986; Daza-losada et al., 2007), and long-term effects (Llorente-Berzal et al., 2013; Lopez-Rodriguez et al., 2014). Another important aspect is

that, in people, most drug use begins in adolescence, and drug use in adolescence is more likely to lead to drug abuse in the adulthood (Grant & Dawson, 1998; Lessem et al., 2006). It is known that adolescence is a highly vulnerable developmental period for the consequences of exposure to drugs of abuse (Schneider, 2008). Moreover, in relation with stress, different studies have shown that stress in adolescence increase the risk for drug abuse (Hoffmann et al., 2000; King & Chassin, 2008; McCormick, 2010). Social interactions are highly rewarding in adolescence (Carpenter-Hyland & Chandler, 2007; McCormick, 2010) and social stress can influence adolescent and adults in different ways (Schramm-Sapyta et al., 2009; Garcia-Pardo et al., 2014).

Ethanol (EtOH) is the most common legal drug consumed among adolescent people, according to data from ESTUDES (Encuesta Estatal sobre el Uso de Drogas en Enseñanzas Secundarias) 2012/2013 and recent studies demonstrated that social stress can enhance its effects (Lopez & Laber, 2014; Karkhanis et al., 2014; Norman et al., 2014; Rodriguez-Arias et al., 2014). Moreover, the combination of legal and illegal drugs is evident among consumers, and MDMA is frequently used in combination with EtOH (Barrett et al., 2006; Breen et al., 2006) and an important percentage of consumers of ectasy (98%) admitted to taking it with alcohol (Rodriguez-Arias et al., 2011; Do Couto et al., 2011). For this reason, it is important to evaluate the effects of both drugs separately and, in future studies, the effects of their combination.

The main objective of the present thesis is to determinate the influence of social stress in the effects of illegal and legal drugs (MDMA and EtOH) using as the main paradigm CPP, although other paradigms have been used such as, second order or two-bottle choice (to study relevant

variables in the drug addiction such as motivation), elevated plus maze (EPM), tail suspension test, passive avoidance, Hebb-Williams maze, etc. Morever, we have researched the involvement of the age variable (adolescence or adult life) and the role of the different neurotransmissor systems (such as glutamate or opioids) in the rewarding effects of MDMA and alcohol.

To sum up, after a wide theoretical framework, different experimental studies will be presented in the next pages, which will to end with a general discussion about the results obtained.

2.- EPIDEMIOLOGY OF MDMA AND ETHANOL CONSUMPTION

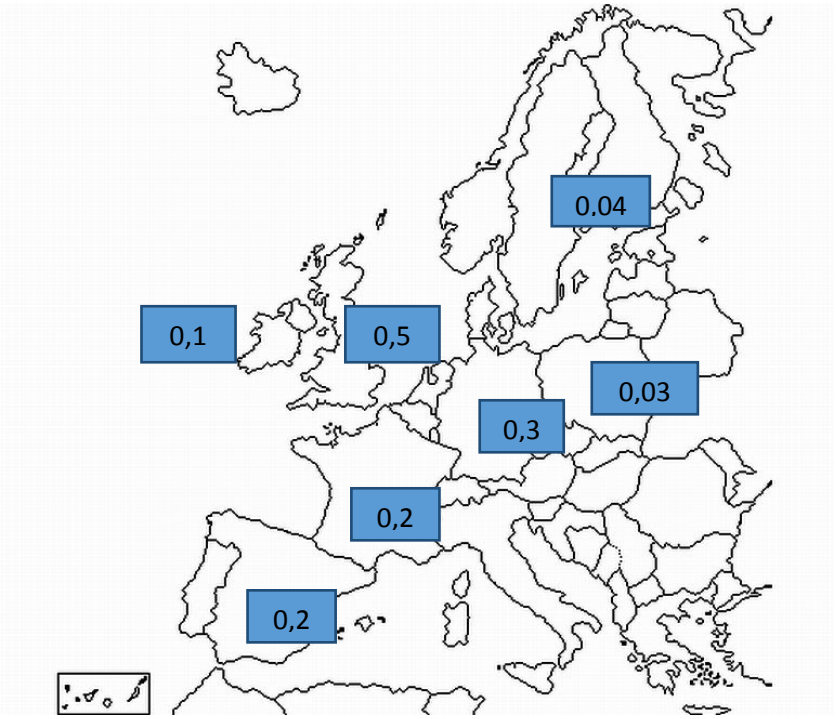
2.- EPIDEMIOLOGY OF MDMA AND ETHANOL CONSUMPTION.

Drug consumption continues to be an important problem in our society. The World Drug Report 2014 elaborated by the Commission on Narcotic Drugs of the United Nations Office on Drugs and Crime (UNODC) reports relevant data about MDMA consumption. E*cstasy* and other amphetamine-type stimulants constitute the second most commonly used group of illicit substances worldwide, with 13.9 million to 54.8 million estimated users.

According to the European Report on drugs 2014 of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *ecstasy* production seems to be concentrated in Belgium and the Netherlands and there are signs of market recovery, after the decrease in the number of laboratories in Europe in 2010-2012. This trend is also reflected in the available data on the content of MDMA tablets analysed, which declined until 2009 and then increased in the last three years of reporting. Nowadays, these data indicates that MDMA is becoming more frequent (see Figure 1). If we focus our attention on the different European countries, the dates show that in 2012 four million *ecstasy* tablets were seized in the European Union, mainly in the Netherlands (2.4 million), followed by the UK (0.5 million) and Germany (0.3 million). In addition to this, Turkey seized 3 million tablets that year.

Figure 1:

Quantities (million tablets) of ecstasy seized 2012 in countries with high values



Source: The European Monitoring Centre for Drugs and Drug Addiction 2014 (EMCDDA).

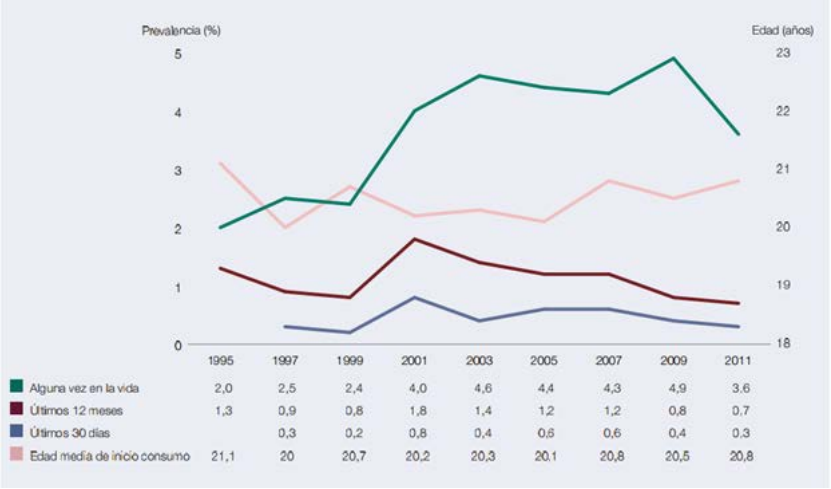
In Spain there are two regular surveys, EDADES (Encuesta Domiciliaria sobre Alcohol y Drogas en España), which polls people aged 15-64 residing in family homes; and ESTUDES (Encuesta Nacional sobre Uso de Drogas en la Enseñanza Secundaria), aimed at students aged 14-18 years who attend Secondary School; both funded and promoted by the

Government Delegation for the National Plan on Drugs (DGPNSD) and Ministry of Health in Spain.

According to the last version of EDADES (1999-2011) published in 2012, a general decline was seen in 2011 in *ecstasy* use prevalence for the usual three time indicators, 3.6% for consumption ever in life, 0.7% for the last 12 months and 0.3% in the last 30 days. This decline is most striking in experimental use (once in life), which is of particular significance, given that *ecstasy* is mainly consumed in this way and considering that in 2009, "Once in a lifetime" consumption rebounded and had the highest prevalence of the time series (4.9%) level. This proportion is down 1.3 percentage points in 2011 to stand at the lowest level of the last decade. However, in relation with the consumption in the last period it is posible to observe an increase again (near to consumption in 2009). Disaggregating by sex and age, it is observed that, as with other illegal substances, consumption of *ecstasy* is more common among men than women, with the highest prevalence (last 12 months) in the group of 15-24 years and 25 to 34 years of age (EDADES 1999-2011) (see figures 2 and 3, for detail). The preliminary report of EDADES 2013 report the same data for consumption in the last 12 months (0.7%).

Figure 2

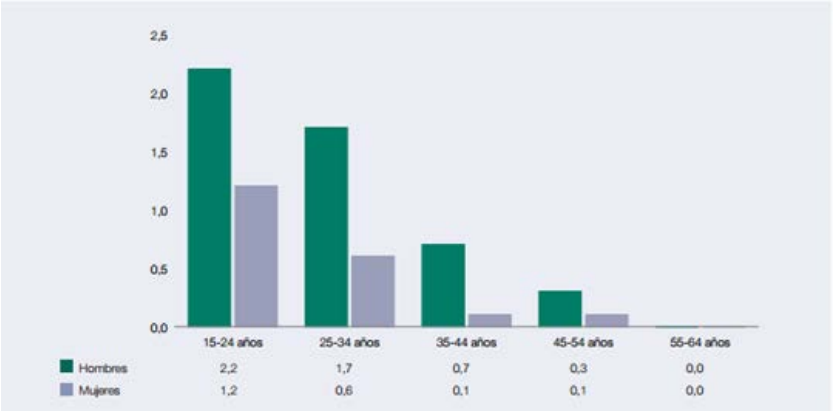
Evolution of the prevalence of ecstasy consumer and average age of first use in a population aged 15-64 (percentages). Spain 1995-



Source: OEDT. Encuesta sobre alcohol y drogas en España (EDADES)

Figure 3

Prevalence of ecstasy in the last 12 months in the population aged 15-64 according to sex and age group (percentages). Spain 2011.

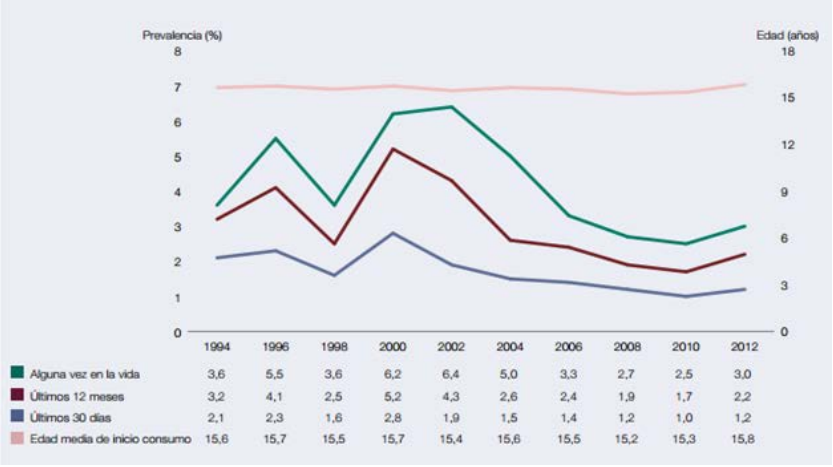


Source: OEDT. Encuesta sobre alcohol y drogas en España (EDADES)

The other epidemiological report ESTUDES (2012/2013) showed that in 2012, the main illegal drugs consumed by students aged 14 to 18 years were cannabis, hypnotics, cocaine and MDMA. Prevalence of *ecstasy* use at least once in life was higher in men than women (3% versus 1,4%), representing an increase of 0.5% compared to 2010. This increase occured mainly among men whose prevalence of consumption doubled that registered among women and the age of first consumption of MDMA was by 15, 8 years of age (see Figure 4).

Figure 4

Evolution of the prevalence of ecstasy and average age of first use among high school students of 14-18 years (percentages).



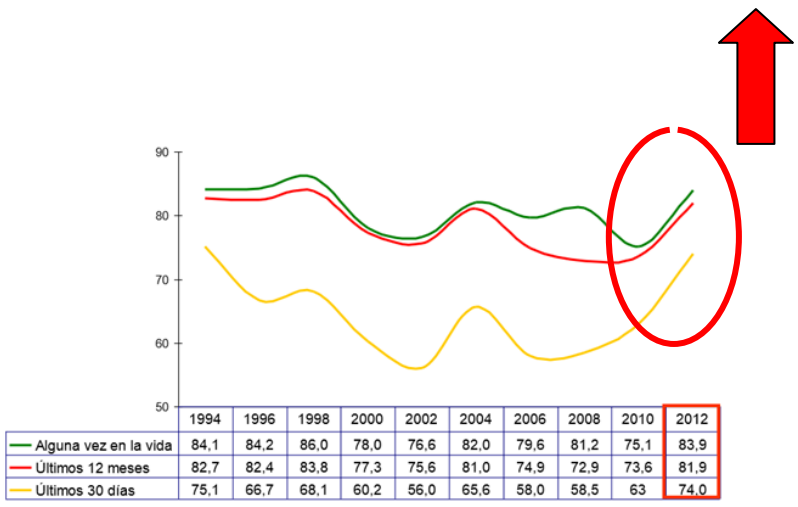
Source: ESTUDES 2012/2013

On the other hand, data about consumption of alcohol shows that it is a problematic topic, mainly among adolescents with binge drinking patterns of consumption. According to data from EDADES the extent of drinking in the Spanish society is practically universal. Thus, in 2013, 93.1% of the Spanish population between 15 and 64 years had consumed at least once in their lives, 78.3% of the population admitted to having consumed in the past year, and 64.4% had done so in the last

month. According to ESTUDES 2012-2013, alcohol is the first legal drug of abuse consumed by adolescents in Spain. In 2012, 81.9% had consumed alcohol in the past year and 74% in the last month. Moreover, the percentage of youth who consumes alcohol remains at high levels: 3 out of 10 in the last month and more than half of the 16 year olds has been drunk in the last year. Related with the binge drinking patterns the data show that this practice increases with age: 4 out of 10 adolescents (14 years) and 8 of 10 (18 years) have a binge pattern of consumption in the last year. The most important aspect in this data is that there is a tendence toward an increase in consumption of alcohol among adolescents (see figure 5).

Figure 5

Evolution of the percentage of alcoholic beverages ESTUDES (2012/2013)



	1994	1996	1998	2000	2002	2004	2006	2008	2010	2012
Alguna vez en la vida	84,1	84,2	86,0	78,0	76,6	82,0	79,6	81,2	75,1	83,9
Últimos 12 meses	82,7	82,4	83,8	77,3	75,6	81,0	74,9	72,9	73,6	81,9
Últimos 30 días	75,1	66,7	68,1	60,2	56,0	65,6	58,0	58,5	63	74,0

Source: ESTUDES 2012/2013. Observatorio español sobre drogas. DGPNSD. MSSSI

3.- ABOUT MDMA....

3.- ABOUT MDMA

MDMA (3,4-Methylenedioxymethamphetamine) belongs to a designer drug group made with different chemical agents. It is an illegal drug well known for its recreational use, primarily because of its empathogenic properties. For example, it increases the feeling of love, sociability, intimacy, confidence, elevated empathy, closeness to others and euphoria (Parrott, 2001; Morgan et al., 2013; Hysek et al., 2014; Davis & Rosenberg, 2014) and it is consumed mainly in places similar to dance club, discos or rave parties where people spend several hours (or even days) dancing in environments with electrical and house music (Bobes et al., 2002). Positive effects after consumption have also been demonstrated in experimental animals, MDMA inducing different changes in social behaviour such as prosocial and anti-aggressive effects (Thompson et al., 2008; Thompson et al., 2009; Machalova et al., 2012).

There are many code names and popular terms for this drug. An early street name, *ecstasy* has give rise to the initials XTC (Shulgin, 1990), but other names are also being used to indicate the same substance (Adam, Essence, lovely drug, “E” or “X”) or "molly" or"mandy" when the drug is in powdered form. The acronym MDM stands for methylene-dioxy-methamphetamine, and MDMA in its full form, are a reference to the initials of the synthetic base 3, 4- methylenedioxymethamphetamine.

3.1.- History

MDMA has been among the most popular illegal psychotropic drugs since the mid 1980s (Kalant, 2001; Freudenmann et al., 2006). However, MDMA was discovered much earlier. MDMA was first synthesized and

patented by the German pharmaceutical company Merck in Darmstadt around 1912, probabily unintentionally, with plans to market a compound very different from MDMA, an appetite suppressor (Freudenmann et al., 2006).

Also, in 1953, MDMA was used by American Army Chemical Centre as a potential brainwashing agent and its toxical effects were evident, althought they were never published. Later, in the 1960s, the longer-acting analogue of MDMA, MDA acquired a recreational use. Its rediscovery in the late 1970s probably had little to do with the fact that it was a legal drug. But its effects were unknown for the moment. In 1978, the biologist and chemist Alexander Shulgin showed the psychoactive effects of MDMA and in 1980s MDMA began to be used as a recreational substance in rave parties among youg people mainly (Pentney, 2001; Sessa, 2007).

As it has been said before, MDMA promotes relaxation, an increase in communication with others, it facililitates a loosening of the ego and encourages elevated thoughtfulness and contemplativeness (Nichols, 1986; Morgan et al., 2013; Hysek et al., 2014). MDMA was also used, sometimes, as a therapy substance. For example, the warmth and feelings of empathy that are experienced under MDMA effects can be used to promote a positive therapy. Utilisation of MDMA as an agent to assist in couples therapy in the United States in the early 1980s was common because it allowed users to approach previously difficult intimate relationship conflicts (Greer & Tolbert 1986; Sessa et al., 2007).

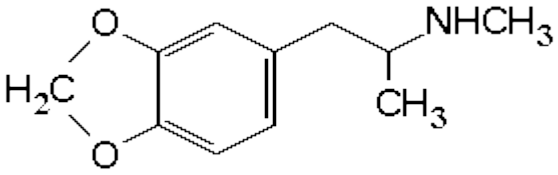
However, years after it appeared, different studies showing addictive effects in MDMA consummers and different neurotoxic effects in rats,

dogs or non human-primates (Mokler et al., 1987; Frith et al., 1987; Ricaurte & McCann, 1992). In fact, in 1985 the "Drug Enforcement Administration" (DEA) included MDMA in the list I of controlled substances showing that MDMA had a wide potencial as an addictive substance and it did not meet the reglamentary norms required by the "Food and Drug Administration". In this decade, several studies have shown the same perspective about the dangers of consuming MDMA and other amphetamines (Ricaurte et al., 1985; Stone et al., 1986; Schmidt, 1987; Commins et al., 1987; Battaglia et al., 1987; Ricaurte et al., 1988; O'Hearn et al., 1988; Pentney, 2001) and argues against its administration in therapy (Parrot, 2012a; Parrot, 2013a; Parrot, 2014a; Parrot, 2014b) while others maintained that *ecstasy* ´s negative effects continue being a controversial topic and support the therapeutic potential of MDMA (Cole, 2014; Doblin et al, 2014).

3.2.- Structure

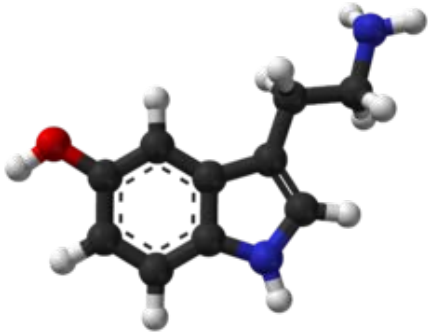
MDMA has a particular structure and although there are other drugs (mainly amphetamines) with similar structure it is clearly stands apart from other hallucinogenic amphetamines, such as DOB (2,5-dimethoxy-4-bromoamphetamine) or DOM (2,5-dimethoxy-4-methylamphetamine) (Morimoto et al., 1998) in that it is a secondary amine. That is, the basic nitrogen is substituted with an N-methyl, while hallucinogenic amphetamines are most potent as primary amines (Nichols & Oberlender, 1989). The molecular formula for MDMA is $C_{11}H_{15}NO_2$.

Figure 6



Chemical structure of MDMA

Figure 7



Dimensional structure of MDMA

3.3.- Composition

Although MDMA is a designer (not natural) drug, the precursors of this substance are vegetables that suffer differents forms of adulteration to produce its addictive properties. In its pure form it is a powder, but in

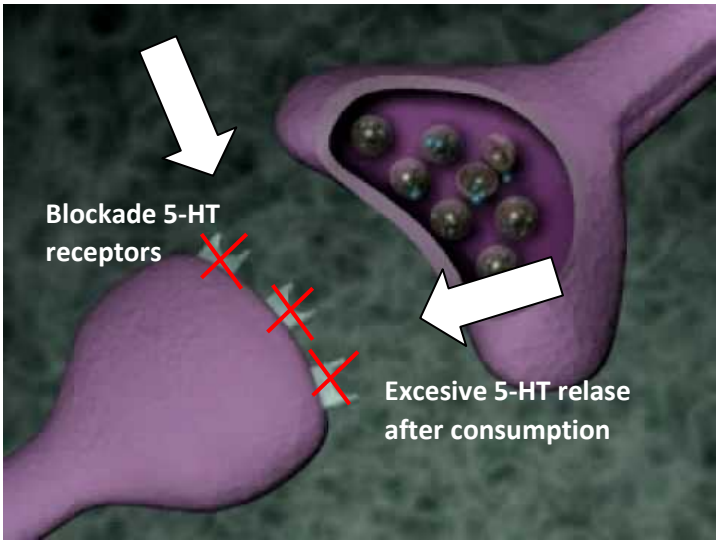
the street it is presented in tablets with different shapes, textures and colours. In Spain, according to data from the Instituto Nacional de Toxicología (INT) the amount of active ingredients present in the seized samples (tablets or capsules of approximately 300 mg) is only between 90 and 166 mg. Normally, MDMA is adulterated with other drugs or their derivates (cannabis, benzodiazepines or methilphenidate). Sometimes, other substances with compounds very different from MDMA are considered *ecstasy*, making it a risky aspect about consumption (Sherlock et al., 1999; Baggott et al., 2000; Cole et al., 2002). Other dangerous effects of MDMA are related with the dose. Lethal doses are above 500 mg, although there have been lethal cases with lower doses. A low-middle dose is considered to be between 50-160 mg and a high hose 180-200 mg (Kalant, 2001). The price in the ilegal market osciles between 5 and 10 euros (data by EMCDDA, 2014). Therefore, it is not very expensive for adolescent and young adults to acquire and it is easy for them to buy the drug in the street.

3.4.- Mechanism of action of MDMA

The effects of MDMA in the central nervous system (SNC) are diverse because this substance interacts with different neurotransmission systems (Breivik et al., 2014; Yubero-Lahoz et al., 2014; Liechti, 2015). The acute effects of MDMA on brain neurotransmitter systems have been well documented. MDMA blocks the serotonine (5-HT), dopamine (DA), and noradrenaline (NA) transporters and stimulates the release of monoamines by reverse transport, mainly 5-HT (Figure 8), NA and DA (Breivik et al., 2014; Colado et al., 2004; Lizarraga et al., 2015), in

several regions of the brain mainly in the nucleus accumbens (NAcc) (Yamamoto & Spanos, 1988; Marona-Lewicka et al., 1996; White et al., 1996; Kankaanpää et al., 1998). Data shows crucial and distinct involvement of the 5-HT system in processes related with drug addiction and compulsive behaviour (Müller & Homberg, 2015). In fact, differents studies have attributed its locomotor and rewarding effects to both the activation of serotonergic and dopaminergic systems (Meyer, 2013; Müller & Homberg, 2015), although other systems like endocannabinoid seem to be also associated (Valverde & Rodriguez-Arias, 2013).

Figure 8



Mechanism of action of MDMA

Glutamatergic system also plays an important role in the mechanism of action of MDMA. Microiontophoretic application of MDMA has been shown to inhibit glutamate evoked firing of most cells in the NAcc (White et al., 1994). Anneken & Gudelsky (2012) reported that in the hippocampus MDMA produces a delayed and sustained increase in the extracellular concentration of glutamate. The MDMA-induced increase in hippocampal glutamate release was suppressed by fluoxetine and the 5-HT2 antagonist ketanserin but was still evident in the presence of tetrodotoxin (a lethal neurotoxin with rapid and potent action) and the authors concluded that 5-HT, released by MDMA, activates 5-HT2A/C receptors, thereby promoting this release of glutamate in the hippocampus.

3.5.- Long-term neurotoxicity and related behavioural alterations

Ecstasy exerts its acute effects by increasing the extracellular concentration of monoamines in the brain by reversing the functions of reuptake mechanisms and these elevations in extracellular monoamine concentrations result in serious damages for the organism, elicit significant neurobehavioral adverse effects, and they can induce even neurotoxicity and neuroinflammation (Parrott, 2002; Ricaurte et al., 2003; Cadet et al., 2007; Capela et al., 2009; Mueller et al., 2011; Torres et al., 2011; Mueller et al., 2013; Parrot, 2013b; Benningfield & Cowan, 2013; Halpin et al., 2014).

In rats, the pharmacological actions of MDMA lead to the long-term loss of 5-HT nerve terminals (Commins et al., 1987; O'Hearn et al., 1988) and biochemically the damage is reflected by a substantial decrease in the

concentration of 5-HT and its metabolite, 5-hydroxyindolacetic acid (5-HIAA) (Colado et al., 1993; Lew et al., 1996; Colado et al., 1997; Shankaran & Gudelsky, 1998; O'Shea et al., 1998; Aguirre et al., 1998; Wallace et al., 2001; Green et al., 2003; Thompson et al., 2004) and a reduction in the density of 5-HT transporter, a hallmark of 5-HT nerve terminal integrity (Colado et al., 1995; O'Shea et al., 1998; Teixeira-Gomes et al., 2014; Halpin et al., 2014).

In mice, repeated administration of *ecstasy* induces dopaminergic neurotoxicity, decreasing the functionality of DA transporters, and produces lasting impairments in recall of alternation behaviour, reducing cognitive flexibility (Viñals et al., 2013). MDMA-induced neurotoxicity can be responsible for cognitive impairment involving different areas in the brain, such as the limbic and cortical regions (Costa et al., 2014).

Similars results were found in non-human primates (Banks et al., 2008) and in baboons (Szabo et al., 2002) with reductions in brain serotonin transporters (SERT) after a treatment with a MDMA dose of 40 mg/kg during 4 days.

Studies in humans through brain imaging, using either positron emission tomography (PET) or single photon emission computed tomography (SPECT), and measuring brain SERT levels as an indicator of neuronal integrity, have suggested that MDMA abusers have damage in serotonergic neurons, with reduced levels of 5-HIAA and SERT densities (McCann et al., 1998; Semple et al., 1999; Reneman et al., 2001; McCann et al., 2005; Parrot, 2012a; Parrot, 2013b). A classical study showed that density of 5-HT2A postsynaptic receptors was lower after

recent abuse, but higher in former *ecstasy* abusers (Reneman et al., 2001), probably as consequence of the wide reduction in serotonin induced by MDMA. Imaging studies have shown lowered brain SERT binding in current MDMA users but it is uncertain for how long this abnormality might persist following abstinence (Selvaraj et al., 2009).

3.6.- Pharmacology of MDMA

MDMA and other amphetamines are rapidly absorbed following oral administration in the form of a pill commonly (Gouzoulis-Mayfrank & Daumann, 2009). MDMA is detectable in the blood within 30 minutes, reaches its max within 1-2 hours after consumption and has a half life of about 6–8 hours (Green et al., 2003; Dumont & Verkes, 2006), althought its effects can be biochemically detected 24-48 hours after consumption (Curran, 2000). The psychoactive effects last for approximately 2–4 hours in spite of persisting blood levels and objective impairment of mental functioning lasting longer than the subjective effects in concordance with the persisting MDMA levels (Lamers et al., 2003). Approximately 40 hours are needed in order for 95% of MDMA to disappear. This is why some consumers describe psychological and physical effects days after consumption (Kalant, 2001).

In rodents or other non-human primats (Chu et al., 1996; Mueller et al., 2008), as well as in humans (de la Torre et al., 2000) the pharmacokinetic of MDMA is nonlinear and MDMA is one of the most dangerous drugs. In effect, (Schifano et al., 2010) analysed the government data on recreational stimulant deaths in the UK between 1997 and 2007 and found that over this period, there were 605

recorded deaths related to *ecstasy*/MDMA. The pharmacokinetics and metabolism of MDMA are described in more detail in other works (de la Torre et al., 2000; Green et al., 2003).

3.7.- Effects of MDMA

The physiological and psychological effects of MDMA are thoroughly described in several studies (Dumont & Verkes 2006; Parrott, 2013 a). There are broad data about the effects of MDMA in the organism because it acts in several parts. So, we will organize the next section in different areas. First we will describe the physiological and behavioural effects of MDMA in humans and then the same effects in experimental animals.

A.- HUMANS

∞ Physiological effects

MDMA administration in humans evidences salient cardiovascular and neurologic sympathomimetic effects. Increased blood pressure and pulse rate and vasoconstriction are commonly observed, as also are diaforesis, mydriasis, dry mouth, jaw clenching, trismus, and bruxism (for this reason, MDMA consumers have baby pacifiers in raves parties). Fatalities can result from cardiac arrest, brain seizure, 'rhabdomyolysis' or the destruction of skeletal muscle tissue, and 'disseminated intravascular coagulation' or the failure of blood clotting which results in uncontrollable bleeding through multiple sites (Henry et al., 1992;

Hall & Henry, 2006; Parrot, 2013a; Michael White, 2014). These symptoms are known as serotonin syndrome.

Another characteristic effect of MDMA is the reduction in local cerebral blood flow and hyperthermia (Parrott, 2012 b; Kiyatkin et al., 2015), that is the major acute adverse event that can follow ingestion of MDMA by recreational users (Parrott, 2013 a). Most people report feeling hot, with pronounced sweating and feelings of dehydration (Parrott et al., 2008) and some consumers even said that they felt like their body was at 115 grades (Cohen, 1998).

These physiological effects, have sometimes been associated with the places where MDMA is consumed, such as dance clubs, dicos or parties, where the ambient temperature is high and where some *ecstasy* users dance for prolonged periods with minimal breaks (Suy et al., 1999; Parrott et al., 2006). Other medical problems are related with hyperthermia including myoglobinuria, renal failure, liver damage and disseminated intravascular coagulopathy (Green et al., 2003; Docherty & Green, 2010; Halpern et al., 2011; Parrott, 2012 b). Such problems can be fatal and are identical to those seen in persons suffering from heatstroke (Kalant, 2001).

MDMA can enhance some aspects of acute and chronic stress in humans. MDMA led to an increase in the levels of cortisol (Harris et al., 2002). Gerra et al., (2003) reported that baseline cortisol was significantly lower in abstinent *ecstasy* users compared with non-user controls and that they displayed reduced cortisol responses to stress, which might indicate a neuroendocrine dysfunction induced by repeated MDMA use. Acute *ecstasy* use increases cortisol levels by 100-200% in drug-free

regular *ecstasy* users, whereas *ecstasy* consumed at dance clubs induces an 800% increase in cortisol levels, because of the combined effects of the stimulant drug and dancing. Also, in three-month abstinent users the cortisol levels were 400% higher than those in controls. Chronic users show heightened cortisol release in stressful environments accompanied by deficits in complex neurocognitive tasks. So, acute and subchronic MDMA increase cortisol levels and induce changes in the hypothalamus-pituitary-adrenal (HPA) axis (Parrot et al., 2014).

∞ Psychological effects

MDMA consumers report increased subjective feelings of love, euphoria, intimacy, personal closeness, elevated vigor and arousal (Liechti et al., 2000 a, b; Kuypers et al., 2007). Psychological effects of MDMA depend on 5-HT, while the euphoric effects appear to relate to DA (Liechti & Vollenweider, 2001). In fact, some consumers have entactogenic effects and positive responses such as feeling like 'floating, flying, highly sensual' and that 'everyone is your friend'.

MDMA, associated with a subjective feeling of confusion that could be related to its serotonergic-induced hallucinogenic effects, seems to have some deleterious effects on psychomotor performance (De la torre et al., 2000). Different reviews with meta-analytic studies indicated that *ecstasy* users are significantly impaired compared to non-consumer subjects on psychomotor performance (Kalechstein et al., 2007; Zakzanis et al., 2007). MDMA increases motor activity in humans and prolongs physical activity (e.g., dancing) when used in nightclubs, increasing the chances for hyperthermia (Gilpin et al., 2011).

One of the most prominent adverse effects of MDMA is related to cognitive functioning (Parrot, 2013 b; Wagner et al., 2014). Memory is an important capacity frequently reported to be affected by MDMA (Verkes et al., 2001; Verbaten, 2003; Daumann et al., 2004; Camarasa et al., 2012; Gallagher et al., 2014). Heffernan et al., (2001) reported a prospective memory damage in MDMA consumers that can persist after acute consumption because Parrott & Lasky (1998) demonstrated that 1 and 4 days after MDMA administration the users have significantly lower scores than controls (60–70% recalled fewer words) on the memory recall task.

Using Wechsler Adult Intelligence Scale memory subscales in a small group of abstinent *ecstasy*/MDMA users, Krystal et al. (1992) found mild to moderate levels of impairment in memory. In the same line, (Morgan, 1999) reported significantly poorer prose recall in abstinent *ecstasy* users, compared to non-user controls. Fox et al., (2002) administered the Cambridge Automated Neurocognitive Test Battery to abstinent *ecstasy* consumers and reported a cognitive function similar to patients with brain damage (problems in a temporal lobe). Also, with a battery of cognitive tasks Reay et al., (2006) found various deficits (including complex decision-taking) in MDMA users. Not surprisingly, long-term MDMA use impairs performance in other cognitive domains diferent to memory such as complex attention (McCann et al., 1999; Gouzoulis-Mayfrank et al., 2000).

Negative emotional states have been described after MDMA consumption, such as increases in self-rated apprehensiveness, depression, and other negative moods (Bedi et al., 2010; Parrott et al., 2011; Kirkpatrick et al., 2012; Taurah et al., 2014). With recreational

consumption of *ecstasy*, acute negative reactions sometimes occur. For example, acute feelings of anxiety, overstimulation, panic, and loss of personal control (Davison & Parrott, 1997; Cohen, 1998). Positive and negative mood changes often develop in the same individual, with feelings of happiness and depression, and extraversion and introversion, during the same *ecstasy*/MDMA experience (Liechti et al., 2000 a, b). In relation with aggression, Reid et al., (2007) reported that those with a higher prevalence of lifetime *ecstasy* use exhibit higher levels of aggressive and violent behaviour. Individuals with low self-control appear to be most affected by *ecstasy* use maybe because aggression is a behaviour related with 5-HT.

B.- EXPERIMENTAL ANIMALS

∞ Physiological effects

In general terms, it is well known that while administration of higher doses of MDMA usually causes hyperthermia in rats and rodents, in some conditions it can also induce hypothermia, particularly following a low dose, or when animals are housed alone or at a cool ambient temperature (Docherty & Green, 2010). Both MDMA- induced hyperthermia and hypothermia result primarily from monoamine release in the brain (Docherty & Green, 2010; Shortall et al., 2013). On the other hand, changes in the cardiovascular system have been descrided after MDMA consumption, which causes tachycardia and arrhythmias (O´Cain et al., 2000; Badon et al., 2002). Administration of MDMA is also associated with alterations in the immune system (de Paula et al., 2008), rendering the animal treated with MDMA more

susceptible to infectious diseases (Boyle & Connor, 2010). Finally, exposure to MDMA decreases levels of gonadotrophin release hormone in the hypothalamus and serum testosterone (Dickerson et al., 2008).

∞ Behavioural effects

MDMA produce an increase in motor activity in rats (Balogh et al., 2004; Cassel et al., 2004; Colussi-Mas & Schenk, 2008; Rodsiri et al., 2011) and mice (Itzhak et al., 2003; Daza-Losada et al., 2008; 2009a; Ferraz-de-Paula et al., 2011), but decrease this behaviour in non-human primates (Taffe et al., 2006; Von Huben et al., 2007).

On the other hand, exposure to a wide range of drugs has been shown to produce an enduring change in behavior termed sensitization. Behavioral sensitization refers to the augmentation of the psychomotor effects of drugs following repeated intermittent exposure and represents a striking form of behavioral plasticity determinated by consumption of drugs (Ball et al., 2011). MDMA produces behavioral sensitization (Ramos et al., 2004; Ball et al., 2006, 2009, 2010). For example, after 10 or 15 days of withdrawal of repeated MDMA treatment, a sensitization of locomotor activity was evident after an MDMA challenge (Ball et al., 2011; Varela et al., 2011). A recent study demonstrated that rats that had a significantly larger locomotor response to the first MDMA injection developed tolerance to the locomotor-activating effects of MDMA instead sensitization. Moreover, while rats that develop sensitization maintained relatively stable levels of MDMA SA over days and did not show cue-induced reinstatement of MDMA-seeking following extinction, rats that developed tolerance

displayed an escalation of MDMA SA and cue-induced reinstatement of MDMA seeking (Ball & Slane, 2014).

With regard to anxiety, MDMA induces mainly an anxiogenic action in animals, but this result depends on the dose, the species of animals and the method used for evaluating anxiety. Low doses (4-8 mg/kg) induce anxiogenic effects and high doses (10mg/kg-20mg/kg) induce anxiolytic effects (Ho et al., 2004; Ferraz-de-Paula et al., 2011). In addition, an anxiolytic effect has been observed after acute treatment with cocaine plus MDMA in mice (Daza-Losada et al., 2009a) or 3 weeks after this combination (Daza-Losada et al., 2008).

MDMA, though considered a prosocial drug, has been shown to have both anxiogenic and anxyolitic effects on social interaction in rodents after acute administration. In mice, the effects of MDMA on social behaviour have been studied by confronting MDMA-treated individuals with an anosmic "standard opponent" in a social encounter that takes place in a neutral area. On the other hand, in rats, different studies have reported increases in anxiety undergoing the social interaction test following several weeks of withdrawal from an MDMA dosage regimen that caused modest serotonergic neurotoxicity (Morley et al., 2001; Gurtman et al, 2002; McGregor et al., 2003). Thus, an anxiogenic profile in the social interaction test has been associated with the long-term depletion of serotonin when there is abstinence following MDMA binges. On the other hand, high impulsivity and aggression levels seen in MDMA consumers may be due to the damage induced by this drug on the serotonergic neurons.

Administration of MDMA can alter learning and memory in animal models using different species like monkeys, mice and rats (Taffe et al., 2001; Moyano et al., 2004; Daza-Losada et al., 2009a; Plaza-Zabala et al., 2010; Camarasa et al., 2012; Shariati et al., 2014). Plaza-Zabala et al. (2010) demostrated that mice treated with MDMA showed reduced learning and recall of active avoidance task when compared with saline-treated controls. Functional deficits in learning/memory have been observed long-term after repeated administration of MDMA in experimental animals including monkeys (Taffe et al., 2001), rats (Skelton et al., 2006) and mice (Trigo et al., 2008). Daza-Losada et al. (2009a) reported that only the high doses of MDMA (20 mg/kg) induce impairments in passive avoidance test. More recently, Abad et al. (2014) showed that after binge administration of MDMA to adolescent rats a neurotoxic damage of hippocampal serotonergic terminals was observed. However, MDMA treatment under restricted conditions of learning and memory (associated with the training of a difficult water maze) increases brain-derived neurotrophic factor (BDNF) expression, stimulates synaptic plasticity and facilitates learning of a water maze task.

4.- ABOUT ALCOHOL....

4.-ABOUT ALCOHOL

Alcohol is the most socially accepted and most commonly used drug of abuse, and it is also the one that induces the most social and health-related problems (Nutt et al., 2010).

EtOH, the main component of alcoholic drinks, is the name for a chemical compound known as ethyl alcohol that in normal conditions is a colorless and flammable liquid with a boiling point of 78.4°C. The concentration of EtOH is variable according with the elaboration of the drink. There are two main categories that are different for their amount of alcohol: fermented beverages (such as beer or wine) with a low graduation (5-10º), and distilled beverages (for example, gin, vodka or whiskey) with a high graduation (40º - 50º).

EtOH affects the CNS, causing disinhibition, confusion, dizziness, euphoria, low glare, drowsiness, and poor motor coordination. In some cases, it increases irritability and aggressiveness. At higher concentrations, it slows movement and causes temporary loss of vision and visual hallucinations (for example, double vision is very typical in drunk people). If the dose of intoxication is very high, it can provoke coma and death.

Disinhibition and sedative effects are characteristic because EtOH is an allosteric modulator of many transmembrane receptors (Pohorecky & Brick, 1988) and it works as a CNS depressant, potentiating the action of γ-amino-butyric (GABA) at the GABA A receptor (Suzdak et al., 1986).

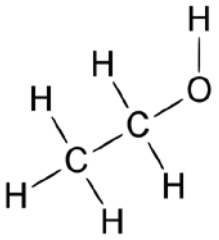
4.1.- History of ethanol

Alcohol is the oldest drug of abuse used by people. For centuries, alcohol consumption has been part of our culture and society. Anciently, drinks with alcohol, have been linked with the divine by its nature and its effects and soon were associated with religious rituals. Later, the consumption of alcohol continued to extend, and nowadays, EtOH is the most important drink in our lives, even in different cultures, in spite of knowing its negative effects.

4.2.- Structure of ethanol

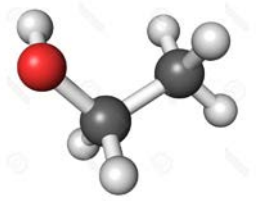
EtOH is a primary alcohol because it has the hydroxyl group connected to a primary carbon atom. EtOH has a lot of polarity because there are several links between oxygen and hydrogen neighboring molecules. Its chemical formula is CH3-CH2-OH (C2H6O).

Figure 9



Chemical structure of ethanol

Figure 10



Dimensional structure of ethanol

4.3.- Pharmacokinetics of ethanol

EtOH is consumed orally. In the body, it is distributed more easily in aqueous media in lipid and it can access the bloodstream from different organs. Once absorption of alcohol has already ocurred, it is distributed in the body, and since it is a water-soluble molecule, it is distributed easily. Moreover, EtOH crosses the blood-brain barrier. In this way EtOH represents a toxic that is rapidly and completely absorbed in the intestinal tract being distributed to most tissues and organs (Szalontay, 2014). The average duration of gastric EtOH absorption process has been estimated at 1.7 minutes. In any case, this time also depends on the dose, because when it increases, the absorption time is also increased. Differences in the distribution of EtOH between individuals are due to different body fat ratio, even when the amount of the substance ingested and body weight are identical, since solubility of EtOH is different in water and in lipid media (Dasgupta, 2015). Differences in the absortion on EtOH between women and men have also been observed (Dettling et al., 2008).

4.4.- Mechanism of action of ethanol

The form of actuation of EtOH in the brain is a controversial topic because alcohol has a complex mechanism of action. EtOH acts on several neurotransmitter systems such as gabaergic, glutamatergic, serotonergic, cannabinoid, opiod or dopaminergic. It is well known that EtOH is an inhibitor substance for the brain and the main neurotransmissor involved is GABA, but it is not the only one. In

addition, EtOH affects most other neurochemical and endocrine systems (Erdozain & Callado, 2014).

*Ethanol and the GABAergic system.

Primarily, γ-amino-butyric (GABA) is considered the main inhibitory neurotransmitter in the CNS. The GABAergic system plays an important role in the mechanism of action of EtOH, mediating different behavioural and pharmacological effects (Erdozain & Callado, 2014). EtOH allosterically potentiates the actions of GABA, stimulating the flow of chloride through the GABAA receptors (Grobin et al., 1998; Aguayo et al., 2002). Chronic EtOH consumption and repeated EtOH withdrawal produce many adaptations of the GABAA receptor function. For instance, after chronic exposure to EtOH different behaviours (like sedative, motor incoordinating and cognitive-impairing effects) are modified due to changes in the sensitivity of GABAA receptor-mediated responses (Silvers et al., 2003; Erdozain & Callado, 2014). EtOH also enhances the GABAB induced synaptic responses being important for example, in the altered mental and motor performance after an acute EtOH intoxication (Federici et al., 2009).

*Ethanol and glutamatergic system

Glutamate is the principal excitatory neurotransmitter in the brain and plays a crucial role in the pharmacological effects of the EtOH (Erdozain & Callado, 2014). Glutamate receptors can be divided into different groups according to the mechanism by which their activation gives rise to a postsynaptic current. There are three types of ionotropic glutamate receptors: NMDA (N-methyl-D-aspartic acid), AMPA (α-amino-3-

hydroxyl-5-methyl-4-isoxazole-propi onic acid), and kainate (Traynelis et al., 2010; Chandrasekar, 2013). The effect of EtOH over the glutamatergic systems lays on the modulation of the ionotropic glutamate receptors. Particularly the NMDA receptors are the most sensitive to the effects of EtOH (Dodd et al., 2000), being its depressant effects based on the antagonism of glutamate action at these receptors (Grobin et al., 1998; Wirkner et al., 1999).

EtOH inhibits the long-term potentiation phenomenon, which is important in learning and memory, probably through NMDA receptors (Givens, 1995). In the alcoholic brain, glutamatergic abnormalities have been observed, such as a lack of glia in the prefrontal cortex of alcoholics (Miguel-Hidalgo & Rajkowska, 2003; Miguel-Hidalgo et al., 2006; Smith et al., 2014). Also, blocking NMDA receptors decreases EtOH reinforcement and inhibits the expression of dependence that confirmed the role of the NMDA receptor and glutamatergic neurotransmission in EtOH reinforcement and dependence (Krystal et al., 2003). Recently, it has been demonstrated that alterations occur in the intrinsic electrical membrane properties and enhanced glutamatergic synaptic transmission in the NAcc core of rats during protracted withdrawal from chronic intermittent EtOH treatment, a model of alcohol dependence (Marty & Spigelman, 2012).

*Ethanol and dopaminergic system

According to Koob & Volkow (2010), the anatomical core of the reward system are dopaminergic neurons of the ventral tegmental area (VTA) that project to the different important structures, such as, NAcc, amygdala or prefrontal cortex and other forebrain structures. Various

techniques have indicated that the mesolimbic DAergic system is activated when alcohol is administered to laboratory animals (Spanagel, 2009) and it has been suggested that the mesocorticolimbic DA system is involved both in the positive and negative reinforcing effects of EtOH (Ericson et al., 2009).

In particular, the VTA is involved in the effects of alcohol. It has been suggested that acute alcohol administration increases extracellular DA within the NAcc via changes in GABAergic feedback into the VTA (Spanagel, 2009). Low systemic doses of EtOH produce a dose-dependent increase in the firing rate of DAergic neurons, and alcohol stimulates DA transmission in the mesolimbic pathway (Gessa et al., 1985; Di Chiara & Imperato, 1988). Genetic factors are important since EtOH-induced DA release is greater in rats bred for alcohol preference (Bustamante et al., 2008), and alcohol SA produces a considerably greater relative stimulation of mesolimbic DA release in alcohol-preferring than in control rats (Katner et al., 1996; Bell et al., 2006). Moreover, alcohol cue-evoked DA release in the ventral striatum is greatest in men with a higher genetic risk for alcoholism (Oberlin et al., 2013).

The involvement of the DA system in the rewarding effects of EtOH is also described in the section 5 (page 60-61).

*Ethanol and the endocannabinoid system

This system participates in drug reward through the release of endocannabinoids in the VTA. Accumulating evidence indicates a central role for the endocannabinoid system in the regulation of the rewarding properties of drugs of abuse including alcohol (Maldonado et al., 2006; Solinas et al., 2007; Serrano & Parsons, 2011; Erdozain & Callado, 2011; Filbey & DeWitt, 2012). Neuroadaptation to chronic EtOH involves changes in the endocannabinoid system (Vinod & Hungund, 2005). The agonism of the endocannabinoid system increases EtOH intake (Linsenbardt & Boehm, 2009) while the cannabinoid receptor 1 (CB1) antagonist rimonabant reduces the increase in DA in the NAcc induced by acute etanol (Cheer et al., 2007), blocks the rewarding effects of alcohol and prevents reinstatement (Parolaro & Rubino, 2008). These results confirm that CB1 contributes to the motivational and reinforcing properties of EtOH, and chronic consumption of EtOH alters the levels of endocannabinoids and CB1 expression in the brain nuclei associated with addiction pathways (Pava & Woodward, 2012).

*Ethanol and opioid system

EtOH reinforcement mechanisms also involve the endogenous opioid system. EtOH may alter opioidergic transmission at different levels and several studies suggest that mu and delta opioid receptors, as well as the enkephalins and beta-endorphins, play a major role in the effects of EtOH (Gianoulakis, 2009; Nutt, 2014). Similarly, kappa opioid receptors (KORs) are involved in the consumption, withdrawal, and escalation of EtOH (Zhou et al., 2013; Faisal et al., 2014). EtOH increases NAcc levels

of endorphins (Olive et al., 2001) and dynorphin (Marinelli et al., 2006). Moreover, chronic alcohol exposure caused changes of the dynorphin system in the brain of alcohol dependent rats and humans (Shippenberg et al., 2007; D'Addario et al., 2013) and it has been suggested that following discontinuation of alcohol administration the increased level of dynorphins may induced a negative emotional state, with craving and negative-reinforcement when alcohol becomes available (Walker & Koob, 2008a, 2008b; Wee & Koob, 2010; Nutt, 2014).

Opioid antagonists can have a potential therapeutic role in alcoholism (Walker et al., 2012; Heilig & Schank, 2014; Nutt, 2014). The administration of mu opioid antagonists decreased the release of DA in the NAcc induced by EtOH and its reinforcing effects (Gonzales & Weiss, 1998; Erdozain & Callado, 2014). Indeed, administration of mu and delta antagonists and KOR agonists also attenuated the responding for alcohol in operant paradigms (Henderson-Redmond & Czachowski, 2014). In addition, in alcohol preferring rats, KOR antagonists prevent alcohol SA (Cashman & Azar, 2014).

Naltrexone, a nonselective opiate antagonist with high affinity for the mu-opioid receptor, was approved by the FDA (Food and Drug Administration) in 1993 as a treatment for alcoholism. Naltrexone reverses alcohol-induced DA release in the NAcc in rats, and suppression of operant alcohol-reinforced behavior by naltrexone is associated with attenuation of the alcohol-induced increase in dialysate DA levels in the NAcc (Gonzales & Weiss, 1998; Henderson-Redmond & Czachowski, 2014). GSK1521498, is a novel selective mu-opioid receptor antagonist in clinical development for behavioral and drug addictive disorders (Nathan et al., 2012). GSK1521498 has been

reported to acting more selectively than naltrexone as an antagonist at the mu-opiod receptor. Under conditions of high receptor expression and endogenous receptor activation in celular assays, GSK1521498 has inverse agonist properties, thereby reducing receptor activation in the absence of an exogenous agonist (Giuliano et al., 2012; Giuliano et al., 2013). In an experiment of the present thesis we have studied the effect of this antagonist on the alcohol consumption in rats (Giuliano et al., submitted in Neuropsychopharmacology).

4.5.- Effects of Ethanol

A.- HUMANS

The effects of EtOH in humans are diverse because they are different depending on dose, gender, age, total amount ingested, the speed of consumption, body weight, the presence of food in the stomach or state of mind. Two types of effects have been observed, each with different characteristics: acute effects, caused by the massive intake of EtOH, which are proportional to the blood concentration, and chronic effects caused by excessive and repeated or continued consumption.

∞ Acute physiological and behavioural effects

EtOH is toxic to most systems and tissues in the body, the CNS being the most affected system. At low concentrations (<0.5 g/l), EtOH produces a depression of inhibitory neural control mechanisms. In consequence, behaviours such as pseudoexcitation, feelings of euphoria, optimism or increased sociability are observed. If the dose of EtOH is higher (1-3

g/l), it produces a central depression and the consequence is a general slowing, ataxia, dysarthria, loss of reflexes and sleep. At very high (4-5 and >5 g/l) concentrations EtOH can induce coma or death caused by respiratory depression (Pohorecky & Brick, 1988; Sarasa-Renedo et al., 2014).

∞ Chronic physiological and behavioural effects

The brain is one of the major targets of the actions of EtOH, and heavy alcohol consumption produces significant alterations of the structure, physiology and function of this organ (Harper & Matsumoto, 2005). EtOH produces permanents effects in users, time after consumption, especially if consumption has been continuous over time, such as neuropsychological negative effects, changes in mood, anxiety, depression, confusion, etc. Even in severe cases, psychosis and mental disorders can appear. The Wernicke-Korsakoff syndrome is a mental disorder, caused by a nutritional deficiency or by excessive alcohol abuse, in which memory, learning and other cognitive functions are affected (Kopelman et al., 2009; Ridley et al., 2013; Brion et al., 2014). It has been observed a reduction in weight and volume of the brains of alcoholic people, correlating the degree of brain atrophy with the speed and the amount of alcohol consumed over the course of life (Sutherland et al., 2014; de la Monte & Kril, 2014).

Other physiological systems, such as the gastrointestinal, cardiovascular, immune, and sexual systems modify their activity after alcohol consumption. For example, EtOH induces digestive disorders (such as cirrhosis, hepatitis, gastritis or pancreatitis); heart disease or

hypertension, it also makes people prone to infections, decreases testosterone levels, etc. (Sarasa-Renedo et al., 2014).

Moreover, EtOH consumption is dangerous during gestation because during brain ontogeny alcohol causes irreversible alterations to the brain structure with long-term cognitive, behavioral and physical anomalies, know as fetal alcohol spectrum disorders (Alfonso-Loeches & Guerri, 2011; Moore et al., 2014).

B.- ANIMALS

∞ Acute physiological and behavioural effects

Nowadays a binge-drinking pattern of consumption is typical in adolescent humans. So, a lot of animal studies focus in the acute effects of alcohol binges in adolescent rodents (Pascual et al., 2007; Do Couto et al., 2011; Rodríguez-Arias et al., 2011; Vidal-Infer et al., 2012 b; Pascual et al., 2014; Montagud-Romero et al., 2014). EtOH binges induces inflammatory mediators in the brain by activating glial cells and stimulating intracellular signalling pathways that trigger induction of cytokines, cyclooxygenase-2 (COX-2), inducible NO synthase (iNOS) and neural cell death (Vallés et al., 2004; Blanco et al., 2005; Pascual et al., 2007). Elevated levels of COX-2 and iNOS are observed during excitotoxicity, ischaemia and neural injury (O'Banion, 1999). These changes are associated with neurobehavioural and cognitive deficits because by altering the activity of different ion channels and receptors, alcohol modulates plasticity and synaptic function in the brain (Zorumski et al., 2014).

It has been reported that the acute administration of EtOH before training leads to impairments in memory using different learning tasks, such as fear conditioning (Gulick & Gould, 2009 a, b, c), Morris water maze (Berry & Matthews, 2004), object and spatial recognition (García-Moreno & Cimadevilla, 2012), radial maze (Hoffmann & Matthews, 2001), and avoidance tasks (Gulick & Gould, 2011). Sometimes, these effects are state-dependent learning. For example, (Sanday et al., 2013) showed that the administration of 1.2 g/kg of this drug during pretraining caused memory impairment in mice, which was counteracted by the pretest administration of the same dose, revealing the participation of the state-dependency. Conversely, the administration of a higher dosis eliminated the influence of state-dependency because 2.4 g/kg EtOH led to amnestic effects irrespective of the time of administration (pretraining and/or pretest). Also in mice, Kameda et al. (2007) demostrated that acute EtOH induced learning (1.2-3.0 g/kg) and memory deficits (0.3-3.0 g/kg) at different doses.

With regards to anxiety, EtOH (1 g/kg) produces anxiolytic-like effects in adult rats, using the light-dark box and EPM exploration tests (Pandey et al., 2008; Sakharkar et al., 2012). In the same line, Sanday et al. (2013) demostrated that low and high doses of EtOH (1.2 and 2.4 g/kg) induced anxiolysis. The involvement of epigenetic mechanisms has also been studied, in particular, the function of histone deacetylases (HDAC) and deoxyribonucleic acid (DNA) methyltransferases (DNMT) in differents areas of the brain, like the amygdala and bed nucleus of stria terminalis (BNST) of adolescent rats. The results showed that the lower dose of EtOH (1 g/kg) produced neither anxiolysis, nor inhibited the HDAC and DNMT activities in the amygdala and BNST. Anxiolysis by EtOH was

observed at 2 and 2.25 g/kg, whereas higher doses (2.5 and 3 g/kg) were found to be sedative (Sakharkar et al., 2014).

On the other hand, EtOH has well documented acute effects on motor function. Low doses of ETOH increased locomotion (1.2-1.8 g/kg) while higher doses (2.4-3.0 g/kg) decreased this behaviour (Kameda et al., 2007; Sanday et al., 2013). A recent study demonstrated that the motor and anxiolytic effects of EtOH in adolescent rats are relatively independent (0.5 g/kg exerted significant anxiolytic effects in the EPM in the absence of stimulating effects in the open field). Moreover, adolescents with a higher frequency of rearing behavior in the open field, higher percentage of open arm entries in the EPM, and lower propensity to enter the central area of the opel field exhibited greater EtOH intake (Acevedo et al., 2014).

Behavioural and cognitive symptoms of EtHO are dependent on the age of the animals. Adolescent rats, compared to adults, are less sensitive to the anxiogenic (Doremus et al., 2003), hypnotic (Matthews et al., 2008) and motor impairing effects (White et al., 2002 a, b; Ramirez & Spear, 2010; Van Skike et al., 2010) of acute alcohol. Conversely, adolescent rodents are more sensitive to alcohol-induced hypothermia (Ristuccia & Spear, 2008), althought in general terms EtOH induce hypothermia also in adulthood (Tanchuck-Nipper et al., 2014) an effect that is mediated by sleep rhythms (Damaggio & Gorman, 2014).

∞ Chronic physiological and behavioural effects

Chronic EtOH induces apoptosis in the rat´s brain (Ikonomidou et al., 2000) and episodic alcohol intoxication or binge-type administration increases cell death in the neocortex, hippocampus and cerebellum (Pascual et al., 2007; McClain et al., 2014), and it increases oxidative stress in the brain (Collins & Neafsey, 2012) In adulthood, "alcohol-preferring" rats show reductions in spine density and terminal branching and increases in mush room and multi-headed spines following chronic EtOH drinking and repeated deprivation (Zhou et al., 2007). EtOH exposure predominately causes reductions in medium spiny neurons branching, length, and/or spine density (McMullen et al., 1984; Rice et al., 2012; Zhou et al., 2007). Spiga et al. (2014) also recently reported reductions in thin spines within the NAcc early during alcohol withdrawal in young rats. Similar results have been showed in rabbits (Romero et al., 2013).

Moreover, animals exposed to EtOH during adolescence exhibit long-term behavioral deficits in the adulthood, such as memory impairments in the passive avoidance test, changes in social interaction behaviors and locomotor activity, and an increase of anxiety in EPM (in this late case in combination with MDMA) (Rodríguez-Arias et al., 2011). Also, animals treated with EtOH (alone and with MDMA) showed poor learning in Hebb Williams test (Vidal-Infer et al., 2012 b).

5.- BRAIN REWARD SYSTEM AND REINFORCING EFFECTS OF MDMA AND ALCOHOL

5.- BRAIN REWARD SYSTEM AND REINFORCING EFFECTS OF MDMA AND ALCOHOL

The rewarding properties of natural stimuli and drugs of abuse are mediated by the activation of the brain reward system. The mesocorticolimbic DA system is known to play a major role in appetitive behaviors (Kelley & Berridge, 2002; Wise, 2008; Carlezon & Thomas, 2009; Dalley & Everitt, 2009) and is the main neural substrate of the rewarding effects produced by drugs of abuse (Wise, 1998; McBride et al., 1999). It is originated in the VTA and projecting to the NAcc and to several key cortical loci, including the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and prefrontal cortex (PFC) (Cohen et al., 2002; Everitt & Robbins, 2005; Hyman et al., 2006; Feltenstein & See, 2008; Dalley & Everitt, 2009; Rodriguez-Arias et al., 2013).

Pathological disturbances of the brain DA systems are involved in a number of neurological and neuropsychiatric disorders, including Parkinson's disease, schizophrenia, attention-deficit hyperactivity disorder and drug addiction (Nieoullon, 2002; Goodman, 2008). Alcohol, psychostimulants, nicotine, opioids, and cannabinoids (Chen et al., 1990; Yoshimoto et al., 1992; Pontieri et al., 1996; Koob & Le Moal, 2001) activate the mesolimbic dopaminergic system and increase DA transmission in the NAcc and associated limbic areas (Wise, 2008). On the other hand, there is another important aspect that is necessary to highlight. Drug addiction is an illness not only characterised by a physical stimulus, because sometimes other cognitive superior process such as learning or memory are involved and they influence the circuit system described before. Responses to drugs can acquire motivational significance by being associated with environmental stimuli through

pavlovian conditioning (O'Brien et al., 1998). These drug associated conditioned stimuli (CSs) may then predict drug availability, evoke memories of drug's effects, or of withdrawal, to result in craving even long into abstinence, and, perhaps most importantly, may elicit and maintain the instrumental behaviours of drug seeking and taking (Childress et al., 1999; Garavan et al., 2000; Robbins & Everitt, 2002). Addiction can be understood in terms of pavlovian and instrumental learning and memory processes, and their subversion by the actions of addictive drugs on dopaminergic transmission within corticostriatal systems, that normally mediate learning and memory processes in the context of natural rewards (Robbins & Everitt, 1999; Everitt & Robbins, 2005; Dalley & Everitt, 2009; Everitt 2014). Other structures play a role in drug addiction. For example, PFC is important to take decisions about consumption and it is involved in behavioural inhibition, flexibility, decision-making and cognitive decisions about the negative consequences of consumption while hippocampus is important for remembering different keys associated with consumption (Cohen et al., 2002; Dalley & Everitt, 2009; Everitt, 2014). For example, using CPP it is very evident, because the experimental animals associated the environmental cues with the rewarding effects of the drug after connecting their mesolimibic area with other neuroanatomical structures such as hippocampus (see Figure 11).

In this regard, the main neurotransmissor in MDMA and EtOH reward and addiction is DA although other neurotransmitters, such as serotonin, are also involved (Müller & Homberg, 2015). MDMA increased the release of DA in NAcc that interacts with other neurotransmitters such as 5-HT or GABA (O´Shea et al., 2005; Amato et

al., 2007; Touriño et al., 2008; Reveron et al., 2010; Kehr et al., 2011). Using the CPP paradigm, it has been demonstrated that MDMA produces reinforcing effects in rats (Meyer et al., 2002; Braida et al., 2005; Diller et al., 2007; Feduccia & Duvauchelle, 2008; Catlow et al., 2010) and mice (Daza-Losada et al., 2007; 2009 b; 2011; Manzanedo et al., 2010; Rodriguez-Arias et al., 2010; Do Couto et al., 2011). Using the AA paradigm, MDMA also induces reinforcing effects in rhesus monkeys (Fantegrossi et al., 2002; Lile et al., 2005), rats (Schenk et al., 2007; 2008; 2011; Cornish et al., 2003) and mice (Trigo et al., 2006; 2007; Touriño et al., 2008; Orejarena et al, 2009; 2011; Ruiz-Medina et al., 2011).

It has been demostrated that activation of DA D1-like and D2-like receptors contributes to the maintenance of MDMA SA. The reinforcing effects of MDMA were attenuated by pretreatment with the D1 antagonist SCH 23390 (Daniela et al., 2004) and with D2 receptor antagonist eticlopride (Brennan et al., 2009). Similarly, DA is involved in the rewarding effects of MDMA in the CPP paradigm. The mixed serotonin (5-HT2A)/DA D2) antagonist risperidone, the DA D1 antagonist SCH 23390, the DA D2 antagonist haloperidol, the D2 antagonist raclopride and the DA release inhibitor CGS 10746B block acquisition of MDMA CPP (Vidal-Infer et al., 2012 a; Roger-Sanchez et al., 2013 a).

As regards alcohol, it has been repeatedly reported that this substance induces stimulant and motivational effects in animal models (Camarini et al., 2010; Brabant et al., 2014). Behavioural and biochemical studies have demonstrated that alcohol takes action in central reward areas and enhances DA neurotransmission from neurons of the VTA increasing DA

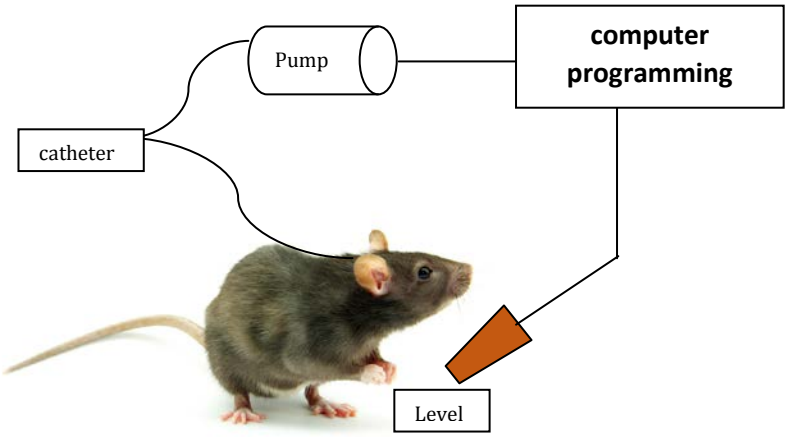
levels within the NAcc and prefrontal cortex (Di Chiara & Imperato, 1988; Boileau et al., 2003; Robinson et al., 2009; Söderpalm & Ericson, 2013; Erdozain & Callado, 2014; Mrejeru et al., 2015). Rodents self-administer EtOH directly in the VTA (Rodd et al., 2004) and the activation of DA receptors in the shell of the NAcc (NAccsh), ventral palid (VP) or medial PFC (mPFC) are involved in mediating the reinforcing effects of EtOH in the VTA, suggesting that the 'alcohol reward' neuro-circuitry consist in the activation of the DA projections in important brain reward areas like VTA, VP and PFC (Ding et al., 2014).

The D1 antagonist SCH 23390 administered into the core or shell of NAcc reduced context-induced reinstatement of EtOH SA (Chaudhri et al., 2009) and the development of EtOH-induced CPP (Pina & Cunningham, 2014). In addition, D2 receptor signaling in the dorsolateral striatum is also involved in EtOH SA (Corbit et al., 2014). Moreover, (Rotter et al., 2012) found that the establishment of EtOH CPP was paralleled by a decrease in frontal cortex DA D2 receptor messenger ribonucleic acid (mRNA) expression. Finally, the DA system is also involved in the rewarding effects of alcohol effects in humans (Charlet et al., 2013).

Figure 11

Most used paradigms of drug reward

a.- Conditioned preference place (CPP)



b.- Intravenous self-administration (SA)

6.- BRAIN STRESS SYSTEM AND DRUG ABUSE

6.- BRAIN STRESS SYSTEM AND DRUG ABUSE

Stress is an internal and external stimulus that can produce changes in our natural organism homeostasis. Stress is a wide term and it can be used for several situations. In fact, a lot of types of stress (physical, emotional, social, pharmacological…) have been described in the literature. Biological and behavioural variables (such as cognition, motivation, emotion) are involved in the stress reaction.

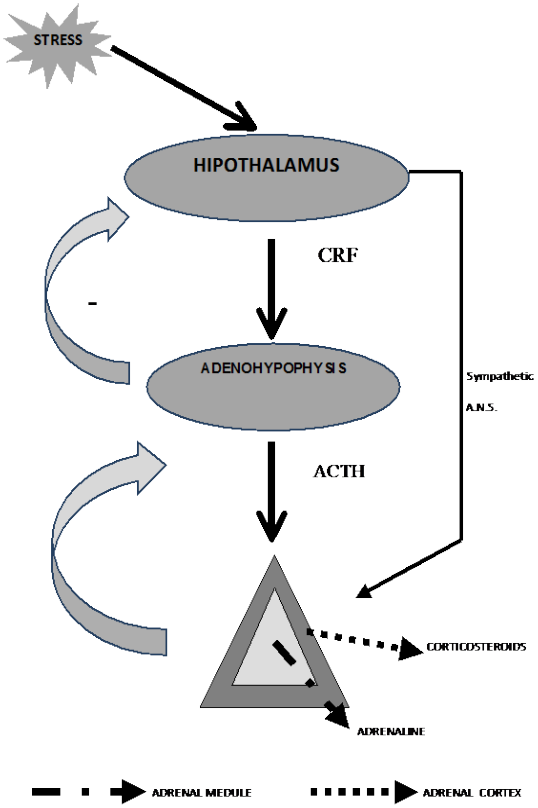
Different regulatory systems of the body are activated during stress situations, but the main structure of central control and regulation is the HPA axis. In response to stress the HPA axis begins different actions in body to go back to homeostasis, including physiological and metabolic changes (Miller & O´Callaghan, 2002), releasing hormones such as corticotropin-releasing factor (CRF), adrenocorticotropin hormone (ACTH) and glucocorticoids; in addition, the symphatic-adrenal system releases catecholamines (adrenaline and NA) (Kupfermann, 1991). Immune system is also involved in stress response (Costa-Pinto & Palermo-Neto, 2010; Capuron & Miller, 2011; Rodriguez-Arias et al., 2013).

Under stress, the HPA axis is activated by the secretion of CRF from the hypothalamus (Turnbull & Rivier, 1997; Sarnyai et al., 2001; Goeders, 2002). CRF-containing neurons projecting from the paraventricular nucleus to the median eminence release the peptide into the adenohypophyseal portal circulation. The binding of CRF to receptors located in the anterior hypophysis results in the synthesis of proopiomelanocortin (POMC), a large precursor protein that produces several smaller peptides, including ACTH and β-endorphin. ACTH

diffuses through the general circulation until it reaches the adrenal glands, where it stimulates the biosynthesis and secretion of adrenocorticosteroids (e.g. cortisol in humans or corticosterone in rodents), which act at diffused body sites to assure the overall response to stress (Goeders, 2003; Kovács, 2013). Under stress, various systems are activated by the effects of cortisol (Chrousos & Gold, 1992; McEwen, 2003). The general function of the HPA axis is controlled by several negative feedback loops (Herman et al., 2012), regulated by mineralocorticoid and glucocorticoid receptors (Harris et al, 2013). Glucocorticoids act in a negative feedback mode by decreasing production and release of CRF in the hypothalamus and of POMC and its neuropeptides in the anterior pituitary (Zhou et al., 2006; Rodriguez-Arias et al, 2013).

On the other hand, in a stressful situation our organism needs to be prepared for acting (the classical flight or fight response) and ensure our survival. For this reason, the sympathetic nervous system activated the adrenal medulla by inducing adrenaline and NA release that produced an increase in heart rate, a rise in blood pressure, a shift in blood flow to the skeletal muscles, an increase in blood glucose, dilation of the pupils and stimulation of respiration (Goeders, 2003). For more information see the next figure.

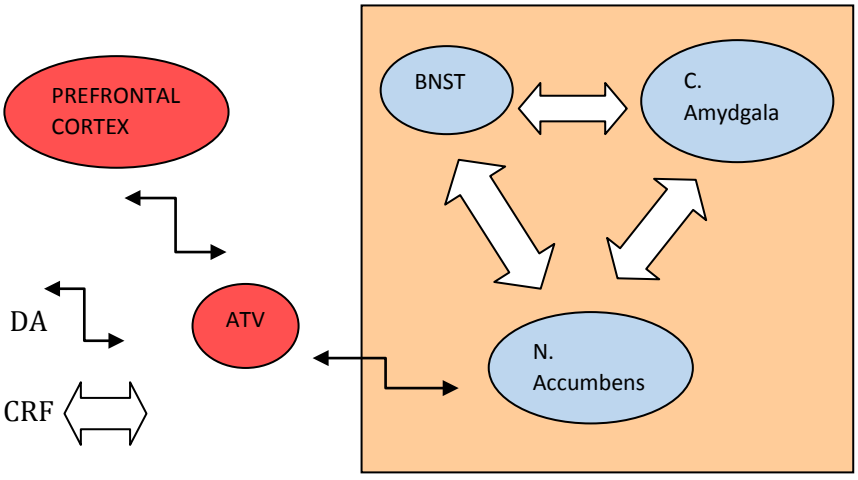
Figure 12: *Pshysiology of the response to stress*



The neurobiological sytems involved in response to stress are close to the neurobiological system involved in drug addiction, the nexus between both systems being the circuitry of the extended amygdala (Koob, 2009; Rodriguez-Arias et al., 2013). Activation of brain stress systems seems to be a key element of the negative emotional state produced by dependence and which drives drug-seeking through negative reinforcement mechanisms (Koob, 2009). Many of the

motivational effects of drugs may involve a common neural circuitry that forms a separate entity within the basal forebrain, termed the "extended amygdala" (Alheid & Heimer, 1988). It has been demonstrated that the extended amygdala circuitry extends from the shell of the NAcc to the BNST and central nucleus of the amygdala (Alheid & Heimer, 1988; de Olmos & Heimer, 1999; Koob, 2009), where neurotransmitters such as CRF, NA, and DA interact. A detailed description of how stress exposure modifies the rewarding effects of drugs of abuse has been reported in Rodriguez-Arias et al. (2013). Moreover, we have performed an exhaustive review of the impact of social stress in addiction to psychostimulants in animal models (see first publication of the present thesis).

Figure 13



Extended amygdala circuitry

7.- ADOLESCENCE, DRUG USE AND STRESS

7.- ADOLESCENCE, DRUG USE AND STRESS

As commented previously, the consumption of drugs, such as alcohol or MDMA, in adolescence is very extended (ESTUDES 2012/2013).

Adolescence refers to the gradual period of behavioral transition from childhood to adulthood but the boundaries of this period are less precisely defined (Spear 2000; Sisk & Foster, 2004). This term is closely related to puberty although the definition is not identical. Adolescence is, in general terms, the period of gradual physiological, cognitive, behavioural and psychological transitions with important changes in life (Pickles et al., 1998; Spear, 2000).

The transition from childhood to adulthood involves extensive developmental changes and reorganisation of the brain (McCormick, 2010). During puberty, neuronal maturation of the brain, which began during perinatal development, is completed such that the behavioral potential of the adult organism can be fully achieved (Schneider, 2008). In relation to these brain changes, there are numerous neurodevelopmental alterations that take place during this period, such as maturational processes in the mPFC and limbic regions, which are characterised by both progressive and regressive changes, e.g. myelination and synaptic pruning (Spear, 2000; Powell, 2006). Maturational changes are also evident during adolescence in limbic regions such as the hippocampus (Wolfer & Lipp, 1995), and gray matter reductions also take place in the striatum and other subcortical structures (Sowell et al., 2002; Rodríguez-Arias & Aguilar, 2012). For this brain reorganisation, adolescence is seen as a highly vulnerable developmental period for the consequences of exposure to drugs of abuse (Schneider, 2008).

Human adolescence is commonly considered to be from 12 to 18 years of age, although the entire second decade of life is sometimes also considered adolescence, with up to 25 years being considered late adolescence (Baumrind, 1987) or young adults. In animals, the period of adolescence is around 21-60 postnatal day (PND), which can be divided into early adolescence, between 21-34 PND, middle adolescence at 34-46 PND and young adults between 46-60 PND (Laviola et al., 2003). Precisely it is in this period when the dates about consumption of EtOH and MDMA mark an important record and there is a sizable research literature using animal models that describes age differences in the effects of drugs of abuse and the underlying mechanisms for the effects of drugs (Barron et al., 2005; Carpenter-Hyland & Chandler, 2007). Furthermore, maturation of neurotransmitter systems such as the glutamatergic, the dopaminergic and also the endogenous cannabinoid system occur during adolescence, with developmental peaks often seen concomitant with the onset of puberty (Rodriguez de Fonseca et al., 1993; Spear, 2000). Basal levels of synaptic DA are lower during this phase of development, although adolescents show a greater and faster increase in drug-induced DA release (Laviola et al., 2001; Badanich et al., 2006). In relation with it, adolescents are generally subject to a less positive impact from stimuli with moderate to low incentive value, and thus seek additional appetitive reinforcers (Spear, 2000). According to differents studies (Bjork et al., 2010) it is shown that in adolescents, important centres of emotions and rewards are very active. For example, amygdala and accumbens of adolescents exhibit more activity than those of adults (Ernst et al., 2011). So, a lot of behaviours described as typicals in adolescence (impulsivity, intake of drugs, desinhibition…) have a biological basis because the adolescents have immature neural

processing in the PFC and other cortical and subcortical regions involved in decision-taking, leading to a behaviour that is biased toward risk and emotional reactivity during the adolescent period (Sturman & Moghaddan, 2011; Rodriguez-Arias & Aguilar, 2012). Many typical adolescent behaviors are very related with the consumption of drugs, such as, risk taking, more autonomy, heightened responsibility, considerable peer influence, impulsivity, egocentrism, shorter periods of sleep, new interests, and increase in the number of conflicts with parents (Spear, 2000; Spear, 2011; Sturman & Moghaddam, 2011). All of these behaviours can lead to a higher incidence of risky behaviours such as a misconduct at school, drink driving, unsafe sex, antisocial behaviours and, of course, use of legal and illegal drugs (Doremus-Fitzwater et al., 2010; Eaton et al., 2012; Spear, 2011).

With regard to stress vulnerability, the adolescent nervous system is more readily shaped by environmental factors like stressful events (McCormick, 2010). In addition, the clinical literature shows that stress in adolescence increase the risk for drug abuse (King & Chassin, 2008; Hoffmann et al., 2000). The effects of stressors on brain structure and function often involve activation of the HPA axis, which results in elevations of glucocorticoid hormone concentrations and increased actions of the hormone at corticosteroid receptors distributed throughout limbic and prefrontal regions of the brain (McCormick, 2010). Elevated exposure to glucocorticoids over the course of adolescence confers sex-specific changes in behavioural responses to drugs of abuse, which may be of relevance for understanding risk factors in people (McCormick, 2010). Behavioral stress affects both the

structure and function of PFC, particularly during infancy and adolescence, though such effects are not necessarily permanent (McEwen & Morrison, 2013). Behavioural experiments in laboratory animals have revealed that adolescents are more disrupted by stressors than younger or older counterparts and that they differ behaviourally and physiologically in their response to stressors when compared to animals of other ages (Stone & Quartermain, 1997; Buwalda et al., 2011). Moreover, while adult male rats, which are repeatedly exposed to daily restraint stress, show a clear habituation in their neuroendocrine response, adolescent male rats actually exhibit a facilitation of this response (Romeo, 2010). For example, studies using physical stress (swim test) show that adolescents are more negatively affected by stressful events than are adults. Compared with adults, adolescent rats show more immobility under stressful situations in this test (Walker et al., 1995). Likewise, studies in laboratory animals have shown that adolescents sometimes exhibit a greater overall hormonal response to stress, evidenced by the increased production of corticosterone, compared with younger animals and a more prolonged increase in stress hormones relative to adults (Spear, 2000).

8.- METHODOLOGY

8.- METHODOLOGY USED IN THIS WORK.

To carry out the different experiments that compose this experimental work, different paradigms have been used with different objectives. The most important has been the conditioned preference place paradigm, which evaluates the conditioned rewarding effects of appetitive natural stimuli and drugs of abuse. The environmental cues can adquire hedonic effects when associated with positive unconditioned stimuli (Tzschentke, 2007; Aguilar et al., 2009; Manzanedo, 2001). CPP phases and procediments are described in detail in the different papers that compose this doctoral thesis (experimental study 1, 2, 3, 6, 7).

Social stress is the other basic procedure in this work. To induce social stress in the animals two different procedures have been used. First, brief or acute agonist encounters with a coespecific mouse in a neutral area have been performed with the result of defeat for the experimental animal (Do Couto et al., 2006; 2009. The second one is the exposure to repeated social defeat (RSD) using the resident/intruder model (Yap et al., 2006; Quadros & Miczek, 2009, Miczek et al., 2011). These different procedures are described in detail in different papers of the present work (experimental study 1, 2, 3, 5, 6, 7).

Also, an important aspect in the drug addiction is the free preference or motivation of the animal to look for the drug. This aspect cannot be directly evaluated in the CPP paradigm, and is especially important when a drug does not induce conditioned reward, for example, EtOH. Thus, the two-bottle choice procedure has been used in this work in different experimental studies because in this paradigm the animal chooses voluntarily whether to consume alcohol or not (Ehringer et al.,

2009; Plescia et al., 2015). A detailed explanation of this procedure can be seen in two works of the present thesis (experimental study 4 and 6).

Finally, also related to the motivation of the animal to consume the drug, second order schedules of drug reinforcement were used in this work. Under the second-order schedules, a reinforcer – usually a drug - is presented according to a schedule in which a more or less extended sequence of responses is reinforced intermittently, for example, following the completion of a fixed ratio (FR) of responses after a fixed interval (FI) has timed out. Completion of each FR is accompanied by the presentation of a stimulus that is contingent to the response, a stimulus that has been previously conditioned by association with the primary reinforcer each time it was presented during earlier training (Everitt and Robbins, 2000; Di Ciano & Everitt, 2005; Giuliano, et al., 2012; Giuliano et al., 2013). This paradigm is described in one paper of the present thesis (experimental study 4).

9.- JUSTIFICATION OF EXPERIMENTS

9.- JUSTIFICATION OF EXPERIMENTS

Taking into consideration that drug addiction is an important problem in our society, that MDMA and EtOH are abuse susbtances with an extended consumption between adolescent and young adults and that stress seems to be an important factor to initiation, maintenance and relapse/reinstatement of the drug addiction, the experiments presented in this doctoral thesis have the general objective to determine how stress exposure can modify the rewarding effects of these drugs and to enhance the knowledge of the neurobiological substrates of these effects.

For this reason, the first step in this work was to do a wide review of all the information available until the moment about the impact of social stress in animal models of drug addiction. The theorical framework (paper 1: Review) was essential to design the experimental work.

Later, we studied the influence of acute social stress on the acquisition of the CPP induced by MDMA and if there were differences between early adolescent and young adult mice (paper 2: experimental study 1).

Then, we determined the role of the glutamatergic NMDA receptors in the acquisition and reinstatement of the rewarding effects of MDMA (paper 3: experimental study 2, in press) as a previous step to evaluate the role of this neurotransmitter system in the influence that acute social defeat has on the rewarding effects of MDMA.

Following, we studied the influence of repeated social stress on the acquisition of the CPP induced by MDMA and if there were differences between early adolescent and young adult mice (paper 4, experimental study 3, submitted).

In paper 5, we report the work made in the Department of Psychology of the Universtiy of Cambridge during a 4-months period of a stay in the prestigious laboratory directed by the professor BJ Everitt. During this time, we studied the effects of opioid system in the alcohol addiction. Then, in relation with our topic, we studied the effects of social stress in the effects of EtOH (see experimental study 6).

In the following study we want to evaluate if the combination of social stress and MDMA use has synergic negative behavioural and cognitive effects because no other paper has studied this relation, even though both drugs induced impairing effects separately. For this reason, after treatment with a high dose of MDMA and exposure to acute social stress, the animals were evaluated in memory, motor activity and depression-like behaviour (experimental study 5, paper in preparation).

As mentioned above, to study how the exposure to acute and repeated social stress affects the motivational effects of ethanol in the CPP paradigm and the voluntary consumption of this drug in the two-bottle choice procedure we design the next study (experimental study 6, paper in preparation).

Finally, to extend the knowledge about the implication of glutamatergic system in the rewarding effects of MDMA, we studied the effects of NMDA and AMPA antagonists, as well as a nitic oxide synthase (NOS) inhibitor, in the CPP induced by *ecstasy*. In addition, we studied the effects of these drugs in mice exposed to acute social defeat before place conditioning with *ecstasy* (experimental study 7, paper in preparation).

The final objective of the present work is to increase our knowledge of the different biological, psychological and environmental factors that contribute to rewarding effects of MDMA and EtOH in mice and translate this knowledge to the prevention and treatment of drug addiction in humans.

10.- PUBLISHED PAPERS

10.- PUBLISHED PAPERS

10.1.- **REVIEW:** Impact of social stress in addiction to psychostimulants: what we know from animal models. Aguilar, M. A, **García-Pardo, M. P.**, Montagud-Romero, S., Miñarro, J., & Do Couto, B. R. *Current Pharmaceutical Design*., 2013;19(40):7009-25. Doi: 10.2174/13816128194013120912 4708

10.2.- **EXPERIMENTAL STUDY 1**: Effects of acute social stress on the conditioned place preference induced by MDMA in adolescent and adult mice. **García-Pardo, M. P.**, Rodríguez-Arias, M., Maldonado, C., Manzanedo, C., Miñarro, J., & Aguilar, M. A. *Behavioural Pharmacology*, 2014 Sep;25(5-6):532-46. Doi: 10.1097/FBP.0000000000000065.

10.3.- **EXPERIMENTAL STUDY 2**: Involvement of NMDA glutamate receptors in the acquisition and reinstatement of the conditioned place preference induced by MDMA. **García-Pardo, M.P.**, Escobar-Valero, C., Rodríguez-Arias, M., Miñarro, J., & Aguilar, M.A . *Behavioural Pharmacology*, 2015, in press.

11.- SUBMITTED PAPERS

11. SUBMITTED PAPERS

11.1.- **EXPERIMENTAL STUDY 3**: Effects of repeated social stress on the conditioned place preference induced by MDMA in adolescent and adult mice. **García-Pardo, M. P.**, Blanco-Gandía, M. C., Valiente-Lluch, M., Rodríguez-Arias, M., Miñarro, J. & Aguilar, M. A . *Submitted to Progress in NeuroPsychopharmacology and Biological Psychiatry (under review)*

11.2.- **EXPERIMENTAL STUDY 4**: A novel preclinical model of alcohol seeking and drinking in alcohol-preferring rats: Selective effects of the novel μ-opioid receptor antagonist GSK1521498. Giuliano, C., Goodlett, C. R., Economidou, D., **García-Pardo, M. P.**, Belin, D., Robbins ,T. W., Bullmore, E. T., & Everitt, B. J. *Submitted to NeuroPsychopharmacology (under second review)*

With regard to this study it is important to note that I have only performed the procedure of the two-bottle choice and the experiments to evaluate the effects of naltrexone and CGS1521498 in ethanol consumption in this paradigm (Figure 4). I have also initiated the second order procedure.

12.- PAPERS IN PREPARATION

12.- PAPERS IN PREPARATION

12.1.- **EXPERIMENTAL STUDY 5**: Cognitive and behavioural effects induced by the combination of social stress and MDMA administration in mice. **García-Pardo, M. P.**, Rodríguez-Arias, M., Miñarro, J., & Aguilar, M. A.

12.2.- **EXPERIMENTAL STUDY 6**: Effects of social stress on the consumption of ethanol in two-bottle choice procedure and on acquisition of ethanol-induced place conditioning in adult mice. **García-Pardo, M. P.**, Rodríguez-Arias, M., Miñarro, J., & Aguilar MA. (in preparation b)

12.3.- **EXPERIMENTAL STUDY 7**: Implication of NMDA and AMPA glutamatergic receptors and nitric oxide (NO) pathway in the rewarding effects of "*ecstasy*" in the conditioned preference place in young adult mice and its modulation by social defeat stress. **García-Pardo, M. P.**, Rodríguez-Arias, M., Miñarro, J., & Aguilar ,M. A. (in preparation c)

13.- RESULTS AND LINE OF ARGUMENT

13.- RESULTS AND LINE OF ARGUMENT

In developed societies, drug consumption is widely extended between adolescent and young subjects (ESTUDES, 2012; EDADES, 2013; EMCDDA, 2014; UNODC, 2014). Alcohol is the legal drug most commonly consumed by adolescents and adults in Europe while MDMA is an illegal drug frequently consumed between adolescents and young adults at weekend parties and discos. Most people used these drugs in a recreational way, but several numbers of individuals showed important problems or damages associated with drug consumption and developed dependence and addiction disorders. Although alcohol and MDMA use is very extended, only some people suffer a transition from the voluntary consumption of these drugs to dependence and addiction, characterized by loss of control over the use of the substance and the enhanced vulnerability to relapse after periods of abstinence (Everitt & Robbins, 2013). Biological as well as individual and environmental variables contribute to the transition to drug addiction, like genetics (Demers et al., 2014), alterations in DA and glutamatergic sytems (Van den Oever et al., 2012; Pierce & Wolf, 2013; Quintero, 2013; van Huijstee & Mansvelder, 2015), age at the moment of drug exposure (Schramm-Sapyta et al., 2009; Doremus-Fitzwater et al., 2010; Gulley & Juraska, 2013), personality traits such as impulsivity or novelty-seeking phenotype (Jupp & Dalley, 2014; Everitt, 2014), social environment (Neisewander et al., 2012) and stress exposure (Sinha et al., 2011; Rodríguez-Arias et al., 2013), between others. Thus, it is essential to know the neurobiological substrate of the rewarding effects of drugs of

abuse and determine which variables are involved in the individual vulnerability to drug addiction. With this objective, in the present thesis we have studied, using different animal models, the influence of some variables, such as age, social stress exposure and pharmacological manipulations, on the rewarding effects of MDMA (commonly known as *ecstasy*) and alcohol (EtOH).

The results obtained in the different experiments performed have increased the knowledge of neurobiological bases of the rewarding effects of MDMA and alcohol. The original findings of our work are: 1. age is an essential factor for the acquisition of the rewarding effects of MDMA in the CPP paradigm; MDMA induces CPP at lower doses in young adults than in adolescent mice. 2. social stress induces acute and long-term effects on the CPP induced by MDMA; social defeat immediately before conditioning decreased CPP, while RSD three weeks before conditioning increased the duration of CPP and the vulnerability to reinstatement; 3. social stress, and its combination with MDMA, induced behavioural alterations that suggested an increased vulnerability to develop anxiety, depression, social avoidance and cognitive impairment; 4. acute and repeated social stress blocked the conditioned place aversion induced by alcohol and increased its intake in the two-bottle choice 5. N-metil-D-aspartato (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors and nitric oxide (NO) pathway are involved in the conditioned rewarding effects of MDMA and modulates the influence of acute social defeat on these effects; 6. alcohol intake in the two-bottle choice paradigm is reduced by the mu opioid antagonist GSK1521498. We hope

that an effective translation of this new knowledge in the next years may contribute to the advance in the prevention and treatment of drug addiction disorders.

Age is an important factor in determining the rewarding effects of drugs of abuse (Schramm-Sapyta et al., 2009; Doremus-Fitzwater et al., 2010; Gulley & Juraska, 2013). Although MDMA is consumed by adolescents or young adults in the context of weekend parties, no previous studies had evaluated the influence of age in the rewarding effects of MDMA in animal models. With this purpose we used mice of two different ages: adolescent and young adult mice. In two different studies of the present thesis we have observed that young adult mice are more sensitive to the rewarding effects of MDMA than adolescent mice in the CPP paradigm. A dose of 1.25 mg/kg of MDMA that is ineffective to induce CPP in adolescent mice (Daza-Losada et al., 2009b; Manzanedo et al., 2010; Rodríguez-Arias et al., 2010; Roger-Sánchez et al., 2013a; García-Pardo et al., 2014) induces such effect in adult mice (García-Pardo et al., 2014; Mateos-Garcia et al., 2015; García-Pardo et al., submitted). Moreover, after conditioning with 10 mg/kg of MDMA adult mice showed reinstatement of CPP with lower doses (2.5 mg/kg) than younger mice (García-Pardo et al., 2014; García-Pardo et al., submitted). These results are in accordance with those of epidemiologic studies reporting that MDMA consumption increases with age in subjects between 14 and 18 years of age (ESTUDES, 2012) and that young adults are the main consumers of MDMA (EDADES, 2011, 2013).

As the maturation of control brain systems in the PFC through adolescence is contextually dependent, recurrent adverse episodes of stress might shape the adolescent brain and trigger long-term maladaptive responses increasing addiction risk (Bernheim et al., 2013). It has been demonstrated that adverse life experiences may render individuals more prone to abuse addictive substances and more vulnerable to relapse into drug-seeking after periods of detoxification (Caprioli et al., 2007; Miczek et al., 2008; Le Moal, 2009; Sinha et al., 2011), being stress a risk factor for the initiation, maintenance and escalation of drug consumption and for relapse (Sinha, 2008; Koob, 2010; Sinha et al., 2011; Logrip et al., 2011, 2012; Aguilar et al., 2013; Rodríguez-Arias et al., 2013). As emotional stressors are primary activators of a stress response in humans, social defeat in an agonistic encounter is considered a stressor of ecological and ethological validity in rodents (Tornatzky & Miczek, 1993) that closely mimics real life situations in a human context (Neisewander et al., 2012). The main objective of the present thesis has been to study the influence of social defeat stress in the effects of MDMA and EtOH. With this purpose, we used two different procedures to induce social defeat in mice allowing the evaluation of both the acute and long-term effects of social defeat on the motivational properties of these drugs.

With regard to MDMA, after performing an exhaustive review of all the studies published about the effects of social stress on the rewarding effects of psychostimulants (Aguilar et al., 2013), we find different studies demonstrating that stress exposure, in particular social defeat, increased cocaine and amphetamine SA (Miczek et al., 2008; Quadros &

Miczek, 2009; Miczek et al., 2011; Cruz et al., 2011; Boyson et al., 2011; 2014; Yap et al., 2014; Han et al., 2015) and the rewarding effect of these drugs in the CPP paradigm (McLaughlin et al., 2006; Burke et al., 2011; Hymel et al., 2014); however, the influence of stress on the effects of MDMA had not been previously evaluated. Moreover, the majority of studies about the effects of social defeat on drug vulnerability have been performed only in adult mice. However, it is essential to test the effects of social defeat stress in younger animals, since adolescence is a highly vulnerable developmental period and adolescent rodents are more vulnerable to stressors than younger or older counterparts (Stone & Quartermain, 1997; Vázquez, 1998; Buwalda et al., 2011). Thus, the use of adolescent and young adult mice to test the effects of social defeat in the rewarding properties of MDMA is another essential contribution of the present work. In several studies of the present thesis we observed that both acute and RSD modify MDMA-induced CPP in adolescent and young adult mice, although the effects observed are different in function of the type of social defeat at which the mice are exposed. Acute social defeat experienced immediately before each conditioning session with MDMA reduces the rewarding effects of this drug in young adult mice, without affect CPP in adolescent mice (García-Pardo et al., 2014). We believe that this lack of MDMA CPP observed in young adult mice after exposure to acute social defeat is mainly related with specific features of this procedure of social stress. Firstly, as mice experienced social defeat immediately before each conditioning session with MDMA, the adverse experience of social defeat could reduce the interest in future social interaction and the typical prosocial and euphoric properties of MDMA. Secondly, social defeat is suffered in the context of an agonistic encounter in a neutral area, which could be less stressful than to be

defeated in the cage of a resident. Thirdly, only the short-term effects of social defeat stress are evaluated (48 hours after the last stress exposure). These results pointed out the importance of the temporal schedule of social defeat and testing, in agreement with previous studies with alcohol. While social defeat immediately before access to EtOH SA decreased intake, when there is a delay between social defeat and SA access an increase in EtOH intake is observed (see Neisewander et al., 2012 for review). It has also been reported that social stress induces a general decrease of ongoing behaviour that might interfere with the expression of CPP (Meerlo et al., 1996) and/or the negative experience of defeat may interfere with the positive effects of MDMA impairing the acquisition of CPP. This reduction in the sensitivity of mice to the rewarding properties of MDMA could lead to an increase in the consumption of this drug, thus facilitating the development of drug abuse and dependence.

Conversely, RSD induces a long-term increase in the duration of CPP in both adolescent and young adult mice and an enhancement in the vulnerability to the reinstatement of CPP in adolescent mice (García-Pardo et al., submitted). These results observed after RSD are in agreement with previous studies in which an increase in the rewarding effects of psychostimulants is generally observed after the absence (10 days or more) of RSD stress in a resident-intruder paradigm (Miczek et al., 2008; Quadros & Miczek, 2009; Miczek et al., 2011; Cruz et al., 2011; Boyson et al., 2011; 2014; Yap et al., 2014; Han et al., 2015). Similarly, in a recent study we demonstrated that mice exposed to RSD during adolescence showed an increase in EtOH consumption and motivation

to drink in adulthood (Rodríguez-Arias et al., 2014). In the present study, RSD induces a more potent long-term increase in the rewarding properties of MDMA in adolescent than in young adult mice, increasing the duration of CPP and the priming-induced reinstatement with a very low dose (0.625 mg/kg). It is important to note that the greater effect of RSD in adolescents is observed in spite of social defeat is a lower stressful stimuli for these mice (as measured by corticosterone levels after social defeat that are lower in adolescent than in young adult mice). This clearly indicates the higher vulnerability of adolescent brain to the impact of social stress.

Besides the modification of the rewarding effects of MDMA, we observed that young adult mice exposed to different kinds of social defeat showed several short- and long-term behavioural alterations. In particular, four episodes of social defeat on alternating days impaired memory in the passive avoidance task 5 days after the last episode of social defeat (García-Pardo et al., in preparation a), while exposure to RSD increased anxiety in the elevated plus maze, induced social avoidance and delayed learning of the Hebb Williams maze at least three weeks after the last episode of social defeat (García-Pardo et al., submitted). Even more significant is the fact that the combination of social defeat with MDMA administration induces profound behavioural alterations such as an increase in the time spent in immobility in the tail suspension test (indicative of a depressive-like state), an impairment of memory in the object recognition task and a reduced motor response to priming with MDMA. These results suggested that the MDMA use associated to conditions of social stress might enhance the vulnerability to develop neuropsychiatric disorders (García-Pardo et al., in preparation a).

The results obtained in the present thesis also demonstrated that the effects of social defeat are different in function of the drug of abuse tested. While acute and RSD induces opposite effects on MDMA reward, both procedures induces the same effects on the rewarding effects of other drugs of abuse. In other PhD thesis in course of our laboratory, the effects of the same procedures of acute and RSD on the rewarding properties of cocaine in the CPP paradigm are being evaluated (Montagud-Romero, PhD thesis in preparation). Both acute and RSD induce an increase in the rewarding and reinstating effects of sub-threshold doses of cocaine and in the duration of the CPP induced by effective doses of this drug (Montagud-Romero et al., under review; Rodríguez-Arias et al., submitted). In a similar way, in other studies of the present thesis we have observed the same effects of acute and RSD on the motivational effects of alcohol in the CPP paradigm and on intake of this substance in the two-bottle choice procedure (García-Pardo et al., in preparation b). Although previous studies have evaluated the effects of social defeat on the rewarding properties of alcohol (see Neisewander et al. 2012, for a review) it is impossible to obtain a clear conclusion of how social defeat modifies such effects of alcohol due to the high disparity in the methodology used in the different studies. The most important contribution of our work is the evaluation of the effects of social stress using two kinds of social defeat and two different models for the evaluation of the motivational effects of alcohol, performing the experiments in mice of the same strain and age. Our results clearly demonstrated that social stress exposure induces an acute and long-

term increase in the vulnerability to alcohol consumption, in agreement with previous studies of our laboratory (Rodríguez-Arias et al., 2014).

As commented above, repeated drug consumption induces different brain changes, which initially involve alterations in the DA system but subsequently imply the recruitment of other neurotransmitters that modulate DA mesolimbic activity, such as the opioid (Nutt, 2014) or glutamate systems (Van den Oever et al., 2012; Pierce & Wolf, 2013; Quintero, 2013; van Huijstee & Mansvelder, 2015). Other contribution of the present thesis is the evaluation of pharmacological manipulations that can reduce the rewarding effects of MDMA in the CPP paradigm or alcohol intake in the two-bottle choice procedure. These kind of experiments allow us to increase the knowledge of the neurobiological basis of the rewarding effects of these drugs and to investigate new targets for the pharmacological treatment of vulnerable subjects that develop drug dependence and addiction. We have demonstrated for the first time that the glutamate NMDA receptors are involved in the rewarding effects of *ecstasy* in the CPP paradigm; the blockade of these receptors with memantine interferes with the acquisition of *ecstasy*-induced CPP and with priming-induced reinstatement of this CPP (García-Pardo et al., in press). Although no previous studies have evaluated the role of glutamate on the rewarding effects of MDMA, the results of this study are in agreement with those demonstrating the involvement of glutamate on the rewarding effects of other drugs of abuse (Olive et al., 2012) and they are consistent with the involvement of glutamatergic system in drug addiction (Pomierny-Chamiolo et al., 2014; Tomek et al., 2013). In addition, the idea that glutamate-mediated plasticity may underlie to the long-term vulnerability to relapse of drug

consumption observed in dependent subjects even after long-term periods of abstinence (van Huijstee & Mansvelder, 2015) is supported by the fact that memantine blocks priming-induced reinstatement after extinction of MDMA CPP. The study of the role of other glutamate receptors and the related NO pathway in the rewarding effects of MDMA and in the modulation that social defeat stress induce in such effects have been the subject of other study of this thesis. The results obtained supported that AMPA receptors as well as the NO pathway are involved in the rewarding effects of *ecstasy* since mice treated with the AMPA antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) or the NOS inhibitor 7-nitrohindrazole (7-NI) before conditioning with a low dose of *ecstasy* did not acquire CPP (García-Pardo et al., in preparation c). In addition, we have evaluated the involvement of NMDA and AMPA glutamate receptors and NO pathway in the effects of acute social stress on the CPP induced by *ecstasy*. Our results suggested that glutamate and NO signalling are involved in the reduction of the MDMA CPP induced by acute social defeat since this effect is selectively reversed by low doses of memantine (MEM) and 7-NI. These results are also in agreement with the idea that glutamate system is involved in the behavioural and physiological changes induced by social defeat stress (Krugers et al., 1993; Belozertseva & Bespalov, 1998; Yap et al., 2005; Covington et al., 2008; Popoli et al., 2011).

With regard to alcohol, it is important to note that in spite of the current pharmacological therapies, nowadays there does not exist an effective treatment for all people with alcohol related disorders. We have demonstrated for the first time that the mu-opioid receptor antagonist GSK1521498 markedly reduced both alcohol seeking and voluntary

alcohol consumption, effects that were greater and longer lasting than those of naltrexone, other compound with the same profile clinically used for the treatment of alcohol dependence. The neurobiological relevance of this study is that we have confirmed the role of opioid system in the alcohol dependence, and have pointed out that the intervention on this system, for example that based in the antagonism of mu-opioid receptors, can help in the development of new pharmacotherapies for the alcoholism.

The main objective of the present thesis was to study the influence of social stress on the rewarding properties of MDMA and alcohol. The conclusion is that exposure to social stress induces a clear modification in the rewarding effects of both drugs which lead to the enhancement in the vulnerability to drug addiction. There are some differences in function of age (adolescent or young adult mice), type of social defeat (short- or long-term effects) and drug (MDMA or alcohol). In the case of MDMA, age and type of social defeat are essential factors determining the effects observed. MDMA induces higher rewarding effects in young adults than in adolescent mice; similarly, social defeat induces a greater corticosterone response in young adults than in adolescent mice (García-Pardo et al., 2014; García-Pardo et al., submitted). Acute social defeat did not induce short-term effects in adolescents but clearly reduces the CPP in young adult mice (García-Pardo et al., 2014). Conversely, RSD induces a long-term effect in both adolescent and young adult mice, increasing the duration of CPP; in this case, even RSD in adolescents has more consequences, enhanced the vulnerability to reinstatement of CPP after extinction (García-Pardo et al., submitted).

With regard to alcohol, both acute and RSD induces the same effect in the two different paradigms that we used to evaluate the effects of alcohol (CPP and two-bottle choice). Social defeat reversed the conditioned place aversion induced by EtOH and increased the intake of this substance. These effects suggested that social stress might enhance the rewarding effects of alcohol and so the vulnerability to develop addiction (García-Pardo et al., in preparation b). In addition, we also demonstrated that social defeat induced long-term behavioural alterations (García-Pardo et al., submitted) and that the combination of social defeat and MDMA is a very dangerous condition that increase the vulnerability to develop neuropsychiatric disorders (García-Pardo et al., in preparation a). In future studies we would like to evaluate the effects of combined administration of EtOH with social defeat as well as the consequences of co-administration of both drugs.

Moreover, the present thesis completes a line of research of our laboratory devoted to discover the neurochemical substrates of the rewarding effects of MDMA. In previous studies we have demonstrated the influence of dopaminergic and serotoninergic systems (Vidal-Infer et al., 2012 a; Roger-Sanchez et al., 2013a, 2013b, 2013c; Aguilar et al., 2015). The original contribution of this thesis is the demonstration of the involvement of the glutamatergic system (NMDA and AMPA receptors) and the NO pathway in the rewarding effects of MDMA. We reported for the first time, that the NMDA antagonist memantine inhibited acquisition and blocked priming-induced reinstatement of MDMA CPP (García-Pardo et al., in press). Similarly, we observed that the AMPA antagonist CNQX and the NOS inhibitor 7-NI also inhibited

MDMA CPP (García-Pardo et al., in preparation c). Besides, our results also suggest that these glutamatergic/NO drugs can reverse the impairing effect of acute social defeat on MDMA CPP. Although these results are promising, they must be completed using the RSD procedure in both adolescent and young adult mice. Lastly, the study performed in the University of Cambridge demonstrates that the blockade of mu-opioid receptors with GSK1521498 reduces EtOH intake in the two-bottle choice paradigm (Giuliano et al., submitted). In future studies we would like to evaluate if this drug also reverses the increase in EtOH intake induced by acute and RSD in this paradigm.

The research of the neurobiological consequences of social stress exposure is a priority line of our laboratory. As commented above, the study of the effects of social stress on the rewarding effects of cocaine, MDMA and alcohol have derived into two different PhD theses. We have also demonstrated that RSD during adolescence induces a long-term impairment of brain blood barrier and modifies cocaine CPP and SA (Rodriguez-Arias et al., submitted) and induced changes in the expression of DA receptors. We are now studying the modulation of the effects of social defeat using different pharmacological approaches, such as D1 and D2 DA antagonists, CRF1 and CRF2 antagonists, etc. New promising approaches are being developed in other laboratories to reverse the effects of social stress such as the disruption of reconsolidation (Hymel et al., 2014), and the inhibition of p38 mitogen-activated protein kinase (MAPK), a protein of the cascade of molecular and cellular events activated by stress (Bruchas et al., 2011). Thus, we would like to investigate how these approaches modify the effects of

social defeat on the rewarding effects of drugs. Similarly, the manipulation of oxytocin, an anti-stress neurohormone involved in drug addiction (Lukas et al., 2011; Sarnyai & Kovács, 2014), might be a new strategy to reduce the effects of different kinds of social defeat. Future studies must also to incorporate another paradigms to evaluate the effects of social stress on the rewarding effects of MDMA and alcohol. For example, studies with the SA paradigm would allow to confirm the results obtained with the CPP, i.e. whether adult mice exposed to acute social defeat need to consume higher quantities of MDMA to feel the same rewarding effect that non-stressed animals. Further studies are also necessary to explore if stressed animals have changes in the motivation to get the drug, using for example, the progressive ratio or the second order paradigm. On the other hand, as behavioural traits such as impulsivity or high novelty seeking are significant variables modulating the development of drug addiction (Jupp & Dalley, 2014; Everitt, 2014), it will be interesting to study if the effects of social stress are modulated by these traits and/or if stressed animals became more or less impulsive to get the drug.

While in this work only corticosterone levels in stressed and non-stressed animals have been measured, in future studies we will evaluate changes in the activity of different neurotransmitter systems involved in the rewarding effects of MDMA and alcohol in mice exposed to different kinds of social stress, using different neurochemical techniques such as high performance liquid chromatography (HPLC), western-blot or microdialysis. It has been reported increases in tyrosine hydroxylase (Rodríguez-Arias et al., 2014) and DA signalling in the

mesocorticolimbic pathway (Razzoli et al., 2011) three weeks after RSD. In addition, RSD potentiates DA release after d-amphetamine challenge (Han et al., 2015) and increased extracellular signal-regulated kinases (ERK) phosphorylation in the VTA and the pharmacological inhibition of this effect attenuated the induction of sensitization and escalated cocaine taking induced by RSD (Yap et al., 2014). RSD also increase the expression of the DA cyclic adenosine 3',5'-monophosphate-regulated phosphoprotein-32 (DARPP-32), but not of D1 or D2 receptors, in different brain areas (Jin et al., 2015). Moreover, CRF-DA interactions in the VTA can play a role in the escalation of cocaine intake induced by RSD, that is prevented by CRF1 and CRF2 antagonists (Boyson et al., 2014); enhanced glucocorticoid levels after RSD might influence mesolimbic dopaminergic activity regulating the firing rate of DA neurons via glucocorticoid receptors on medium spiny neurons of the NAcc that also expressed D1 receptors (Spanagel et al., 2014). In addition, different procedures of social defeat induces variations of serotonin levels in brain structures involved in the reward (Jacobson-Pick et al., 2013), a downregulation of the serotonergic gene expression in the Raphe nuclei two weeks after RSD (Boyarskikh et al., 2013), and up-regulates expression of SERT in rat dorsal raphe (Zhang et al., 2012) and of 5-HT(1B) in rostral NAcc shell (Furay et al., 2011). Finally, four 5-min aggressive encounters reduced the mRNA levels of the autoreceptor 5-HT1A in the dorsal raphe leading to hyperactivity of 5-HT neurons (Cooper et al., 2009). Some of these changes might alter reward mechanisms and be involved in the RSD-induced increase in vulnerability to drugs of abuse. Moreover, the knowledge of such changes might contribute to the identification of new drug targets for the treatment of drug addiction.

We consider that the present thesis offers a complete picture of the short- and long-term effects of social defeat on the motivational properties of MDMA and alcohol, making an important contribution to the knowledge on the effects of stress on drug addiction and behaviour. In addition, we have demonstrated the involvement of the glutamatergic system and NO pathway in the rewarding effects of MDMA and have find new pharmacological manipulations that reversed these effects of MDMA (such as NMDA and AMPA receptor antagonists or NOS inhibitor) and EtOH intake (such as the mu-opioid receptor antagonist GSK1521498). Our current objective is to evaluate whether these treatments can also reverse the enhancement of vulnerability to MDMA and alcohol induced by exposure to social stress. Although preliminary, the experiments perform with this objective are promising. In addition, different lines of research are opened from the results obtained in the present thesis. We expect in future years a translation of our basic research to develop better prevention and treatment strategies reducing the negative influence of stress on addictive disorders.

14.- CONCLUSIONS

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* Young adult mice acquired CPP after conditioning with 1.25 and 10 mg/kg of MDMA. Mice did not show CPP after exposure to acute social defeat before each conditioning session with MDMA.

* Adolescent mice showed CPP only after conditioning with 10 mg/kg of MDMA and acute social defeat did not modify the effect of MDMA.

* Social defeat induced a lower stress response in adolescent that in young adult mice since corticosterone levels are enhanced immediately after social defeat only in young adult mice.

* These results suggested that young adult mice are more sensitive than adolescents to the rewarding effects of MDMA and that the stress induced by social defeat in young adult mice interferes with the acquisition of CPP.

* Adolescent and young adult mice exposed to repeated social defeat (RSD) showed a long-term enhancement in their sensitivity to the rewarding effects of MDMA.

* An increase in the duration of the CPP induced by 1.25 and 10 mg/kg of MDMA was observed three weeks after exposure to RSD in adolescent and young adult mice.

* An enhancement of the vulnerability to priming-induced reinstatement was observed in mice exposed to RSD during adolescence and conditioned with 1.25 mg/kg of MDMA.

* The increase in the rewarding and reinstating effects of MDMA in mice exposed to RSD during adolescent is observed despite these mice showed lower levels of corticosterone than young adult mice, indicating the high vulnerability of adolescent brain to stress exposure.

* The conditioned rewarding effects of *ecstasy* in mice depend on the activation of NMDA glutamate receptors. The NMDA antagonist memantine inhibited acquisition of *ecstasy* CPP and blocked priming-induced reinstatement.

* Administration of the mu-opioid receptor antagonist GSK1521498 (0,1, 1, 3 mg/kg) reduced the consumption of alcohol in the two-bottle choice procedure in alcohol-prefering rats, suggesting the usefulness of this compound for the treatment of alcoholism.

* The combination of MDMA (10 mg/kg) with acute social defeat induced cognitive deficits (implicit and recognition memory), depression-like behaviour in the tail suspension test and weak motor response to MDMA priming.

* Acute and RSD reversed the conditioned place aversion induced by alcohol (2.5 g/kg) and increased the voluntary consumption of this substance in the two-bottle choice procedure in mice, suggesting that social stress enhances the rewarding effects of alcohol.

* Besides glutamate NMDA receptors, AMPA receptors and NO pathway are involved in the conditioned rewarding effects of *ecstasy*. Memantine (10 mg/kg), the AMPA antagonist CNQX (0.25, 1 and 5 mg/kg) and the NOS inhibitor 7-NI (7.25 and 12.5 mg/kg) blocked the acquisition of the CPP induced by *ecstasy* in mice.

* Memantine (5 mg/kg) and 7-NI (7.25 mg/kg) reversed the impairing effects of acute social defeat on *ecstasy* CPP, suggesting that glutamate and NO pathway are involved in these effects of social stress.

15.- REFERENCES

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Abad, S., Fole, A., del Olmo, N., Pubill, D., Pallàs, M., Junyent, F., ... & Escubedo, E. (2014). MDMA enhances hippocampal-dependent learning and memory under restrictive conditions, and modifies hippocampal spine density. *Psychopharmacology*, 231(5), 863-874.

Able, J. A., Gudelsky, G. A., Vorhees, C. V., & Williams, M. T. (2006). 3, 4-Methylenedioxymethamphetamine in adult rats produces deficits in path integration and spatial reference memory. *Biological Psychiatry*, 59(12), 1219-1226.

Acevedo, M. B., Nizhnikov, M. E., Molina, J. C., & Pautassi, R. M. (2014). Relationship between ethanol-induced activity and anxiolysis in the open field, elevated plus maze, light-dark box, and ethanol intake in adolescent rats. *Behavioural Brain Research*, 265, 203-215.

Aguayo, L. G., Peoples, R. W., Yeh, H. H., & Yevenes, G. E. (2002). GABA-A receptors as molecular sites of ethanol action. Direct or indirect actions?. *Current Topics in Medicinal Chemistry*, 2(8), 869-885.

Aguilar A, Garcia-Pardo M.P, Montagud-Romero, S., Minarro, J., & Do Couto, B. R. (2013). Impact of social stress in addiction to psychostimulants: what we know from animal models. *Current Pharmaceutical Design*, 19(40), 7009-7025.

Aguilar, M. A., Minarro, J., & Felipo, V. (2000). Chronic moderate hyperammonemia impairs active and passive avoidance behavior and conditional discrimination learning in rats. *Experimental Neurology*, 161(2), 704-713.

Aguilar, M. A., Rodríguez-Arias, M., & Miñarro, J. (2009). Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. *Brain Research Reviews*, 59(2), 253-277.

Aguilar, M. A., Roger-Sánchez, C., Rodríguez-Arias, M., & Miñarro, J. (2015). Cocaine enhances the conditioned rewarding effects of MDMA in adolescent mice. *Brain Research Bulletin*, 113, 27-33.

Aguirre, N., Ballaz, S., Lasheras, B., & Del Rio, J. (1998). MDMA (Ecstasy') enhances 5-HT 1A receptor density and 8-OH-DPAT-induced hypothermia: blockade by drugs preventing 5-hydroxytryptamine depletion. *European Journal of Pharmacology*, 346(2), 181-188.

Al Maamari, E., Al Ameri, M., Al Mansouri, S., & Bahi, A. (2014). Inhibition of urokinase plasminogen activator "uPA" activity alters ethanol consumption and conditioned place preference in mice. *Drug Design, Development and Therapy*, 8, 1391.

Alfonso-Loeches, S., & Guerri, C. (2011). Molecular and behavioral aspects of the actions of alcohol on the adult and developing brain. *Critical Reviews in Clinical Laboratory Sciences*, 48(1), 19-47.

Alheid, G. F., & Heimer, L. (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. *Neuroscience*, 27(1), 1-39.

Ali, S. F., Haung, P., & Itzhak, Y. (2000). Role of peroxynitrite in methamphetamine-induced dopaminergic neurotoxicity and sensitization in mice. *Addiction Biology*, 5(3), 331-341.

Amato, J. L., Bankson, M. G., & Yamamoto, B. K. (2007). Prior exposure to chronic stress and MDMA potentiates mesoaccumbens dopamine release mediated by the 5-HT1b receptor. *Neuropsychopharmacology*, 32(4), 946-954.

Amiri, S., Shirzadian, A., Haj-Mirzaian, A., Imran-Khan, M., Balaei, M. R., Kordjazy, N., ... & Mehr, S. E. (2014). Involvement of the nitrergic system in the proconvulsant effect of social isolation stress in male mice. *Epilepsy & Behavior*, 41, 158-163.

Anderson, K. L., & Itzhak, Y. (2003). Inhibition of neuronal nitric oxide synthase suppresses the maintenance but not the induction of psychomotor sensitization to MDMA ('Ecstasy') and p-chloroamphetamine in mice. *Nitric Oxide*, *9*(1), 24-32.

Anneken, J. H., & Gudelsky, G. A. (2012). MDMA produces a delayed and sustained increase in the extracellular concentration of glutamate in the rat hippocampus. *Neuropharmacology*, 63(6), 1022-1027.

Arias-Cavieres, A., Rozas, C., Reyes-Parada, M., Barrera, N., Pancetti, F., Loyola, S., ... & Morales, B. (2010). MDMA ("ecstasy") impairs learning in the Morris Water Maze and reduces hippocampal LTP in young rats. *Neuroscience Letters*, 469(3), 375-379.

Asl, S. S., Farhadi, M. H., Moosavizadeh, K., Saraei, A. S. K., Soleimani, M., Jamei, S. B., ... & Mehdizadeh, M. (2012). Evaluation of Bcl-2 family gene expression in hippocampus of 3, 4-methylenedioxymethamphetamine treated rats. *Cell Journal (Yakhteh)*, 13(4), 275.

Asl, S. S., Mousavizedeh, K., Pourheydar, B., Soleimani, M., Rahbar, E., & Mehdizadeh, M. (2013). Protective effects of N-acetylcysteine on 3, 4-methylenedioxymethamphetamine-induced neurotoxicity in male Sprague–Dawley rats. *Metabolic Brain Disease*, 28(4), 677-686.

Asl, S. S., Saifi, B., Sakhaie, A., Zargooshnia, S., & Mehdizadeh, M. (2015). Attenuation of ecstasy-induced neurotoxicity by N-acetylcysteine. *Metabolic Brain Disease*, 30(1), 171-181.

Babbedge, R. C., Bland-Ward, P. A., Hart, S. L., & Moore, P. K. (1993). Inhibition of rat cerebellar nitric oxide synthase by 7-nitro indazole and related substituted indazoles. *British Journal of Pharmacology*, 110(1), 225-228.

Badanich, K. A., Adler, K. J., & Kirstein, C. L. (2006). Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. *European Journal of Pharmacology*, 550(1), 95-106.

Badon, L. A., Hicks, A., Lord, K., Ogden, B. A., Meleg-Smith, S., & Varner, K. J. (2002). Changes in cardiovascular responsiveness and cardiotoxicity elicited during binge administration of Ecstasy. *Journal of Pharmacology and Experimental Therapeutics*, 302(3), 898-907.

Baggott, M., Heifets, B., Jones, R. T., Mendelson, J., Sferios, E., & Zehnder, J. (2000). Chemical analysis of ecstasy pills. *JAMA*, 284(17), 2190-2190.

Bahi, A. (2012). The selective metabotropic glutamate receptor 7 allosteric agonist AMN082 prevents reinstatement of extinguished ethanol-induced conditioned place preference in mice. *Pharmacology Biochemistry and Behavior*, 101(2), 193-200.

Bahi, A. (2013)a. Increased anxiety, voluntary alcohol consumption and ethanol-induced place preference in mice following chronic psychosocial stress. *Stress*, 16(4), 441-451.

Ball, K. T., & Slane, M. (2014). Tolerance to the locomotor-activating effects of 3, 4-methylenedioxymethamphetamine (MDMA) predicts escalation of MDMA self-administration and cue-induced reinstatement of MDMA seeking in rats. *Behavioural Brain Research*, 274, 143-148.

Ball, K. T., Budreau, D., & Rebec, G. V. (2006). Context-dependent behavioural and neuronal sensitization in striatum to MDMA (ecstasy) administration in rats. *European Journal of Neuroscience*, 24(1), 217-228.

Ball, K. T., Klein, J. E., Plocinski, J. A., & Slack, R. (2011). Behavioral sensitization to 3, 4-methylenedioxymethamphetamine (MDMA; ecstasy) is long lasting and modulated by the context of drug administration. *Behavioural Pharmacology*, 22(8), 847.

Ball, K. T., Wellman, C. L., Fortenberry, E., & Rebec, G. V. (2009). Sensitizing regimens of (±) 3, 4-methylenedioxymethamphetamine (ecstasy) elicit enduring and differential structural alterations in the brain motive circuit of the rat. *Neuroscience*, 160(2), 264-274.

Ball, K. T., Wellman, C. L., Miller, B. R., & Rebec, G. V. (2010). Electrophysiological and structural alterations in striatum associated with behavioral sensitization to (±) 3, 4-methylenedioxymethamphetamine (ecstasy) in rats: role of drug context. *Neuroscience*, 171(3), 794-811.

Balogh, B., Molnar, E., Jakus, R., Quate, L., Olverman, H. J., Kelly, P. A., ... & Bagdy, G. (2004). Effects of a single dose of 3, 4-methylenedioxymethamphetamine on circadian patterns, motor activity and sleep in drug-naive rats and rats previously exposed to MDMA. *Psychopharmacology*, 173(3-4), 296-309.

Banasikowski, T. J., MacLeod, L. S., & Beninger, R. J. (2012). Comparison of nafadotride, CNQX, and haloperidol on acquisition versus expression of amphetamine-conditioned place preference in rats. *Behavioural Pharmacology*, 23(1), 89-97.

Banks, M. L., Czoty, P. W., Gage, H. D., Bounds, M. C., Garg, P. K., Garg, S., & Nader, M. A. (2008). Effects of cocaine and MDMA self-administration on serotonin transporter availability in monkeys. *Neuropsychopharmacology*, 33(2), 219-225.

Barak, S., Carnicella, S., Yowell, Q. V., & Ron, D. (2011). Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: implications for alcohol reward and seeking. *The Journal of Neuroscience*, 31(27), 9885-9894.

Barber, T. A., Meyers, R. A., & McGettigan, B. F. (2010). Memantine improves memory for taste-avoidance learning in day-old chicks exposed to isolation stress. *Pharmacology Biochemistry and Behavior*, 95(2), 203-208.

Barrett, S. P., Darredeau, C., & Pihl, R. O. (2006). Patterns of simultaneous polysubstance use in drug using university students. *Human Psychopharmacology: Clinical and Experimental*, 21(4), 255-263.

Barron, S., White, A., Swartzwelder, H. S., Bell, R. L., Rodd, Z. A., Slawecki, C. J., ... & Spear, L. P. (2005). Adolescent vulnerabilities to chronic alcohol or nicotine exposure: findings from rodent models. *Alcoholism: Clinical and Experimental Research*, 29(9), 1720-1725.

Battaglia, G., Yeh, S. Y., O'Hearn, E., Molliver, M. E., Kuhar, M. J., & De Souza, E. B. (1987). 3, 4-Methylenedioxymethamphetamine and 3, 4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [3H] paroxetine-labeled serotonin uptake sites. *Journal of Pharmacology and Experimental Therapeutics*, 242(3), 911-916.

Baumrind, D. (1987). A developmental perspective on adolescent risk taking in contemporary America. *New Directions for Child and Adolescent Development*, (37), 93-125.

Bechtholt, A. J., Gremel, C. M., & Cunningham, C. L. (2004). Handling blocks expression of conditioned place aversion but not conditioned place preference produced by ethanol in mice. *Pharmacology Biochemistry and Behavior*, 79(4), 739-744.

Becker, H. C., Lopez, M. F., & Doremus-Fitzwater, T. L. (2011). Effects of stress on alcohol drinking: a review of animal studies. *Psychopharmacology*, 218(1), 131-156.

Bedi, G., Hyman, D., & de Wit, H. (2010). Is ecstasy an "empathogen"? Effects of±3, 4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. *Biological Psychiatry*, 68(12), 1134-1140.

Belin, D., & Deroche-Gamonet, V. (2012). Responses to novelty and vulnerability to cocaine addiction: contribution of a multi-symptomatic animal model. *Cold Spring Harbor Perspectives in Medicine*, 2, a011940.

Bell, R. L., Rodd, Z. A., Lumeng, L., Murphy, J. M., & McBride, W. J. (2006). REVIEW: The alcohol-preferring P rat and animal models of excessive alcohol drinking. *Addiction Biology*, 11(3-4), 270-288.

Belozertseva, I. V., & Bespalov, A. Y. (1998). Effects of NMDA receptor channel blockers, dizocilpine and memantine, on the development of opiate analgesic tolerance induced by repeated morphine exposures or social defeats in mice. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 358(2), 270-274.

Benningfield, M. M., & Cowan, R. L. (2013). Brain serotonin function in MDMA (ecstasy) users: evidence for persisting neurotoxicity. *Neuropsychopharmacology*, 38(1), 253-255.

Bernheim, A., Halfon, O., & Boutrel, B. (2013). Controversies about the enhanced vulnerability of the adolescent brain to develop addiction. *Frontiers in Pharmacology*, 4, 118.

Berry, R. B., & Matthews, D. B. (2004). Acute ethanol administration selectively impairs spatial memory in C57BL/6J mice. *Alcohol*, 32(1), 9-18.

Bjork, J. M., Smith, A. R., Chen, G., & Hommer, D. W. (2010). Adolescents, adults and rewards: comparing motivational neurocircuitry recruitment using fMRI. *PloS One*, 5(7), e11440.

Björkqvist, K. (2001). Social defeat as a stressor in humans. *Physiology & Behavior*, 73(3), 435-442.

Blanco, A. M., Vallés, S. L., Pascual, M., & Guerri, C. (2005). Involvement of TLR4/type I IL-1 receptor signaling in the induction of inflammatory mediators and cell death induced by ethanol in cultured astrocytes. *The Journal of Immunology*, 175(10), 6893-6899.

Bobes J., Sáiz P. A., González M. P., Bascarán M. T., Bousoño M, Ricaurte G. A., &McCann U. D. (2002). Use of MDMA and other illicit drugs by young adult males in northern Spain. A five-year study. *European Addiction Research,* 8(3), 147-54.

Boileau, I., Assaad, J. M., Pihl, R. O., Benkelfat, C., Leyton, M., Diksic, M., ... & Dagher, A. (2003). Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse*, 49(4), 226-231.

Boyarskikh U. A., Bondar N. P., Filipenko M. L., & Kudryavtseva N. N. (2013). Downregulation of serotonergic gene expression in the Raphe nuclei of the midbrain under chronic social defeat stress in male mice. *Molecular Neurobiology*, 48(1), 13-21.

Boyle, N. T., & Connor, T. J. (2010). Methylenedioxymethamphetamine ('Ecstasy')-induced immunosuppression: a cause for concern?. *British Journal of Pharmacology*, 161(1), 17-32.

Boyson, C. O., Holly, E. N., Shimamoto, A., Albrechet-Souza, L., Weiner, L. A., DeBold, J. F., & Miczek, K. A. (2014). Social Stress and CRF–Dopamine Interactions in the VTA: Role in Long-Term Escalation of Cocaine Self-Administration. *The Journal of Neuroscience*, 34(19), 6659-6667.

Boyson, C. O., Miguel, T. T., Quadros, I. M., DeBold, J. F., & Miczek, K. A. (2011). Prevention of social stress-escalated cocaine self-administration by CRF-R1 antagonist in the rat VTA. *Psychopharmacology*, 218(1), 257-269.

Brabant, C., Guarnieri, D. J., & Quertemont, E. (2014). Stimulant and motivational effects of alcohol: Lessons from rodent and primate models. *Pharmacology Biochemistry and Behavior*, 122, 37-52.

Braida, D., Iosue, S., Pegorini, S., & Sala, M. (2005). 3, 4 Methylenedioxymethamphetamine-induced conditioned place preference (CPP) is mediated by endocannabinoid system. *Pharmacological Research*, 51(2), 177-182.

Braida, D., Pozzi, M., Cavallini, R., & Sala, M. (2002). 3, 4 Methylenedioxymethamphetamine (ecstasy) impairs eight-arm radial maze performance and arm entry pattern in rats. *Behavioral Neuroscience*, 116(2), 298.

Breen, C., Degenhardt, L., Kinner, S., Bruno, R., Jenkinson, R., Matthews, A., & Newman, J. (2006). Alcohol use and risk taking among regular ecstasy users. *Substance Use & Misuse*, 41(8), 1095-1109.

Breivik, T., Bogen, I. L., Haug, K. H., Fonnum, F., Opstad, P. K., Eide, D. M., & Myhre, O. (2014). Effects of long-term exposure of 3, 4-methylenedioxymethamphetamine (MDMA;"ecstasy") on neuronal transmitter transport, brain immuno-regulatory systems and progression of experimental periodontitis in rats. *Neurochemistry International*, 72, 30-36.

Brennan, K. A., Carati, C., Lea, R. A., Fitzmaurice, P. S., & Schenk, S. (2009). Effect of D1-like and D2-like receptor antagonists on methamphetamine and 3, 4-methylenedioxymethamphetamine self-administration in rats. *Behavioural Pharmacology*, 20(8), 688-694.

Brion, M., Pitel, A. L., Beaunieux, H., & Maurage, P. (2014). Revisiting the continuum hypothesis: toward an in-depth exploration of executive functions in Korsakoff syndrome. *Frontiers in Human Neuroscience*, 8*, 498*.

Bruchas, M. R., Schindler, A. G., Shankar, H., Messinger, D. I., Miyatake, M., Land, B. B., ... & Chavkin, C. (2011). Selective p38α MAPK deletion in serotonergic neurons produces stress resilience in models of depression and addiction. *Neuron*, 71(3), 498-511.

Burke, A. R., & Miczek, K. A. (2014). Stress in adolescence and drugs of abuse in rodent models: Role of dopamine, CRF, and HPA axis. *Psychopharmacology*, 231(8), 1557-1580.

Burke, A. R., Watt, M. J., & Forster, G. L. (2011). Adolescent social defeat increases adult amphetamine conditioned place preference and alters D2 dopamine receptor expression. *Neuroscience*, 197, 269-279.

Bustamante, D., Quintanilla, M. E., Tampier, L., Gonzalez-Lira, V., Israel, Y., & Herrera-Marschitz, M. (2008). Ethanol induces stronger dopamine release in nucleus accumbens (shell) of alcohol-preferring (bibulous) than in alcohol-avoiding (abstainer) rats. *European Journal of Pharmacology*, 591(1), 153-158.

Buwalda, B., Geerdink, M., Vidal, J., & Koolhaas, J. M. (2011). Social behavior and social stress in adolescence: a focus on animal models. *Neuroscience & Biobehavioral Reviews*, 35(8), 1713-1721.

Byrne, T., Baker, L. E., & Poling, A. (2000). MDMA and learning: effects of acute and neurotoxic exposure in the rat. *Pharmacology Biochemistry and Behavior*, *66*(3), 501-508.

Cadet, J. L., Krasnova, I. N., Jayanthi, S., & Lyles, J. (2007). Neurotoxicity of substituted amphetamines: molecular and cellular mechanisms. *Neurotoxicity Research*, 11(3-4), 183-202.

Caldwell, E. E., & Riccio, D. C. (2010). Alcohol self-administration in rats: modulation by temporal parameters related to repeated mild social defeat stress. *Alcohol*, 44(3), 265-274.

Camarasa, J., Marimón, J. M., Rodrigo, T., Escubedo, E., & Pubill, D. (2008). Memantine prevents the cognitive impairment induced by 3, 4-methylenedioxymethamphetamine in rats. *European Journal of Pharmacology*, 589(1), 132-139.

Camarasa, J., Rodrigo, T., Pubill, D., & Escubedo, E. (2012). Memory impairment induced by amphetamine derivatives in laboratory animals and in humans: a review. *Biomolecular Cconcepts*, 3(1), 1-12.

Camarini, R., Marcos Pautassi, R., Mendez, M., Marian Quadros, I., Lucia Souza-Formigoni, M., & Boerngen-Lacerda, R. (2010). Behavioral and neurochemical studies in distinct animal models of ethanol's motivational effects. *Current Drug Abuse Reviews*, 3(4), 205-221.

Capela, J. P., Carmo, H., Remião, F., Bastos, M. L., Meisel, A., & Carvalho, F. (2009). Molecular and cellular mechanisms of ecstasy-induced neurotoxicity: an overview. *Molecular Neurobiology*, 39(3), 210-271.

Caprioli, D., Celentano, M., Paolone, G., & Badiani, A. (2007). Modeling the role of environment in addiction. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 31(8), 1639-1653.

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology & Therapeutics*, 130(2), 226-238.

Carlezon, W. A., & Thomas, M. J. (2009). Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. *Neuropharmacology*, 56, (S1), 122-132.

Carnicella, S., Amamoto, R., & Ron, D. (2009). Excessive alcohol consumption is blocked by glial cell line–derived neurotrophic factor. *Alcohol*, 43(1), 35-43.

Carpenter-Hyland, E. P., & Chandler, L. J. (2007). Adaptive plasticity of NMDA receptors and dendritic spines: implications for enhanced vulnerability of the adolescent brain to alcohol addiction. *Pharmacology Biochemistry and Behavior*, 86(2), 200-208.

Cashman, J. R., & Azar, M. R. (2014). Potent Inhibition of Alcohol Self-Administration in Alcohol-Preferring Rats by a κ-Opioid Receptor Antagonist. *Journal of Pharmacology and Experimental Therapeutics*, 350(1), 171-180.

Cassel, J. C., Jeltsch, H., Koenig, J., & Jones, B. C. (2004). Locomotor and pyretic effects of MDMA–ethanol associations in rats. *Alcohol*, 34(2), 285-289.

Catlow, B. J., Badanich, K. A., Sponaugle, A. E., Rowe, A. R., Song, S., Rafalovich, I., ... & Sanchez-Ramos, J. (2010). Effects of MDMA ("ecstasy") during adolescence

on place conditioning and hippocampal neurogenesis. *European Journal of Pharmacology*, 628(1), 96-103.

Chandrasekar, R. (2013). Alcohol and NMDA receptor: current research and future direction. *Frontiers in Molecular Neuroscience*, 6, *14*.

Charlet, K., Beck, A., & Heinz, A. (2013). The dopamine system in mediating alcohol effects in humans. In: Geller MA, Ellenbroek BA & and Marsden CA, editors. *Behavioral Neurobiology of Alcohol Addiction,* Springer: Berlin. pp. 461-488.

Chaudhri, N., Sahuque, L. L., & Janak, P. H. (2009). Ethanol seeking triggered by environmental context is attenuated by blocking dopamine D1 receptors in the nucleus accumbens core and shell in rats. *Psychopharmacology*, 207(2), 303-314.

Cheer, J. F., Wassum, K. M., Sombers, L. A., Heien, M. L., Ariansen, J. L., Aragona, B. J., ... & Wightman, R. M. (2007). Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. *The Journal of Neuroscience*, 27(4), 791-795.

Chen, J., Paredes, W., Li, J., Smith, D., Lowinson, J., & Gardner, E. L. (1990). Δ9-Tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. *Psychopharmacology*, 102(2), 156-162.

Childress, A. R., Mozley, P. D., McElgin, W., Fitzgerald, J., Reivich, M., & O'Brien, C. P. (1999). Limbic activation during cue-induced cocaine craving. *American Journal of Psychiatry*, 156(1), 11-18.

Chipan, C., Camarasa, J., Pubill, D., & Escubedo, E. (2008) b. Memantine prevents MDMA-induced neurotoxicity. *Neurotoxicology*, 29(1), 179-183.

Chipana, C., Torres, I., Camarasa, J., Pubill, D., & Escubedo, E. (2008)a. Memantine protects against amphetamine derivatives-induced neurotoxic damage in rodents. *Neuropharmacology*, 54(8), 1254-1263.

Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *JAMA*, 267(9), 1244-1252.

Chu, T., Kumagai, Y., DiStefano, E. W., & Cho, A. K. (1996). Disposition of methylenedioxymethamphetamine and three metabolites in the brains of different rat strains and their possible roles in acute serotonin depletion. *Biochemical Pharmacology*, 51(6), 789-796.

Cohen, C., Perrault, G., Voltz, C., Steinberg, R., & Soubrie, P. (2002). SR141716, a central cannabinoid (CB1) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behavioural Pharmacology*, 13(5-6), 451-463.

Cohen, R. S. (1998). The love drug: marching to the beat of ecstasy. *Haworth Medical Press*, New York.

Colado, M. I., Camarero, J., Mechan, A. O., Sanchez, V., Esteban, B., Elliott, J. M., & Green, A. R. (2001). A study of the mechanisms involved in the neurotoxic action of 3, 4-methylenedioxymethamphetamine (MDMA,'ecstasy') on dopamine neurones in mouse brain. *British Journal of Pharmacology*, 134(8), 1711-1723.

Colado, M. I., Murray, T. K., & Green, A. R. (1993). 5-HT loss in rat brain following 3, 4-methylenedioxymethamphetamine (MDMA), p-chloroamphetamine and fenfluramine administration and effects of chlormethiazole and dizocilpine. *British Journal of Pharmacology*, 108(3), 583-589.

Colado, M. I., O'shea, E., & Green, A. R. (2004). Acute and long-term effects of MDMA on cerebral dopamine biochemistry and function. *Psychopharmacology*, 173(3-4), 249-263.

Colado, M. I., O'shea, E., Granados, R., Murray, T. K., & Green, A. R. (1997). In vivo evidence for free radical involvement in the degeneration of rat brain 5-HT following administration of MDMA ('ecstasy') and p-chloroamphetamine but not the degeneration following fenfluramine. *British Journal of Pharmacology*, 121(5), 889-900.

Colado, M. I., Williams, J. L., & Green, A. R. (1995). The hyperthermic and neurotoxic effects of 'Ecstasy'(MDMA) and 3, 4 methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. *British Journal of Pharmacology*, 115(7), 1281-1289.

Colas-Zelin, D., Light, K. R., Kolata, S., Wass, C., Denman-Brice, A., Rios, C., ... & Matzel, L. D. (2012). The imposition of, but not the propensity for, social subordination impairs exploratory behaviors and general cognitive abilities. *Behavioural Brain Research*, 232(1), 294-305.

Cole, J. C. (2014). MDMA and the "Ecstasy Paradigm". *Journal of Psychoactive Drugs*, 46(1), 44-56.

Cole, J. C., Bailey, M., Sumnall, H. R., Wagstaff, G. F., & King, L. A. (2002). The content of ecstasy tablets: implications for the study of their long-term effects. *Addiction*, 97(12), 1531-1536.

Collins, M. A., & Neafsey, E. J. (2012). Neuroinflammatory pathways in binge alcohol-induced neuronal degeneration: oxidative stress cascade involving aquaporin, brain edema, and phospholipase A2 activation. *Neurotoxicity Research*, 21(1), 70-78.

Collins, S. L., & Kantak, K. M. (2002). Neuronal nitric oxide synthase inhibition decreases cocaine self-administration behavior in rats. *Psychopharmacology*, 159(4), 361-369.

Colussi-Mas, J., & Schenk, S. (2008). Acute and sensitized response to 3, 4-methylenedioxymethamphetamine in rats: different behavioral profiles reflected in different patterns of Fos expression. *European Journal of Neuroscience*, 28(9), 1895-1910.

Commins, D. L., Vosmer, G., Virus, R. M., Woolverton, W. L., Schuster, C. R., & Seiden, L. S. (1987). Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. *Journal of Pharmacology and Experimental Therapeutics*, 241(1), 338-345.

Cooper, M. A., Grober, M. S., Nicholas, C. R., & Huhman, K. L. (2009). Aggressive encounters alter the activation of serotonergic neurons and the expression of 5-

HT1A mRNA in the hamster dorsal raphe nucleus. *Neuroscience*, 161(3), 680-690.

Corbit, L. H., Nie, H., & Janak, P. H. (2014). Habitual responding for alcohol depends upon both AMPA and D2 receptor signaling in the dorsolateral striatum. *Frontiers in Behavioral Neuroscience*, 8, 301.

Cornish, J. L., Shahnawaz, Z., Thompson, M. R., Wong, S., Morley, K. C., Hunt, G. E., & McGregor, I. S. (2003). Heat increases 3, 4-methylenedioxymethamphetamine self-administration and social effects in rats. *European Journal of Pharmacology*, 482(1), 339-341.

Costa, G., Simola, N., & Morelli, M. (2014). MDMA administration during adolescence exacerbates MPTP-induced cognitive impairment and neuroinflammation in the hippocampus and prefrontal cortex. *Psychopharmacology*, 231(20), 4007-4018.

Costa-Pinto, F. A. D., & Palermo-Neto, J. (2010). Neuroimmune interactions in stress. *Neuroimmunomodulation*, 17(3), 196-199.

Cottler, L. B., Womack, S. B., Compton, W. M., & Ben-Abdallah, A. (2001). Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. *Human Psychopharmacology: Clinical and Experimental*, 16(8), 599-606.

Covington III, H. E., Tropea, T. F., Rajadhyaksha, A. M., Kosofsky, B. E., & Miczek, K. A. (2008). NMDA receptors in the rat VTA: a critical site for social stress to intensify cocaine taking. *Psychopharmacology*, 197(2), 203-216.

Cruz, F. C., Quadros, I. M., Hogenelst, K., Planeta, C. S., & Miczek, K. A. (2011). Social defeat stress in rats: escalation of cocaine and "speedball" binge self-administration, but not heroin. *Psychopharmacology*, 215(1), 165-175.

Cunningham, C. L. (2014). Genetic relationship between ethanol-induced conditioned place preference and other ethanol phenotypes in 15 inbred mouse strains. *Behavioral Neuroscience*, 128(4), 430.

Cunningham, C. L., & Henderson, C. M. (2000). Ethanol-induced conditioned place aversion in mice. *Behavioural Pharmacology*, 11(7-8), 591-602.

Cunningham, C. L., & Patel, P. (2007). Rapid induction of Pavlovian approach to an ethanol-paired visual cue in mice. *Psychopharmacology*, 192(2), 231-241.

Cunningham, C. L., Clemans, J. M., & Fidler, T. L. (2002). Injection timing determines whether intragastric ethanol produces conditioned place preference or aversion in mice. *Pharmacology Biochemistry and Behavior*, 72(3), 659-668.

Cunningham, C. L., Gremel, C. M., & Groblewski, P. A. (2006). Drug-induced conditioned place preference and aversion in mice. *Nature Protocols*, 1(4), 1662-1670.

Cunningham, C. L., Henderson, C. M., & Bormann, N. M. (1998). Extinction of ethanol-induced conditioned place preference and conditioned place aversion: effects of naloxone. *Psychopharmacology*, 139(1-2), 62-70.

Cunningham, J. I., Raudensky, J., Tonkiss, J., & Yamamoto, B. K. (2009). MDMA pretreatment leads to mild chronic unpredictable stress-induced impairments in spatial learning. *Behavioral Neuroscience*, 123(5), 1076.

Curran, H. V. (2000). Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. *Neuropsychobiology*, 42(1), 34-41.

D'Addario, C., Caputi, F. F., Rimondini, R., Gandolfi, O., Del Borrello, E., Candeletti, S., & Romualdi, P. (2013). Different alcohol exposures induce selective alterations on the expression of dynorphin and nociceptin systems related genes in rat brain. *Addiction Biology*, 18(3), 425-433.

Dalley, J. W., & Everitt, B. J. (2009). Dopamine receptors in the learning, memory and drug reward circuitry. *Seminars in Cell & Developmental Biology,* 20(4), 403-410.

Damaggio, A. S., & Gorman, M. R. (2014). Circadian phase determines effects of repeated ethanol vapor exposure and withdrawal on body temperature and

activity rhythms of male mice. *Alcoholism: Clinical and Experimental Research*, 38 (3), 879-888.

Daniela, E., Brennan, K., Gittings, D., Hely, L., & Schenk, S. (2004). Effect of SCH 23390 on (±)-3, 4-methylenedioxymethamphetamine hyperactivity and self-administration in rats. *Pharmacology Biochemistry and Behavior*, 77(4), 745-750.

Dasgupta, A. (2015) Alcohol and Its Biomarkers: Clinical Aspects and Laboratory Determination. Chapter 2: Genetic aspects of alcohol metabolism and Drinking Behavior. *Elsevier Science & Technology*, pp. 37-63.

Daumann, J., Fischermann, T., Heekeren, K., Thron, A., & Gouzoulis-Mayfrank, E. (2004). Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. *Biological Psychiatry*, 56(5), 349-355.

Davis, A. K., & Rosenberg, H. (2014). The Prevalence, Intensity, and Assessment of Craving for MDMA/Ecstasy in Recreational Users. *Journal of Psychoactive Drugs*, 46(2), 154-161.

Davison, D., & Parrott, A. C. (1997). Ecstasy (MDMA) in recreational users: self-reported psychological and physiological effects. *Human Psychopharmacology Clinical and Experimental*, 12(3), 221-226.

Daza-Losada, M., Do Couto, B. R., Manzanedo, C., Aguilar, M. A., Rodríguez-Arias, M., & Miñarro, J. (2007). Rewarding effects and reinstatement of MDMA-induced CPP in adolescent mice. *Neuropsychopharmacology*, 32(8), 1750-1759.

Daza-Losada, M., Miñarro, J., Aguilar, M. A., Valverde, O., & Rodriguez-Arias, M. (2011). Acute blockade of CB1 receptor leads to reinstatement of MDMA-induced conditioned place preference. *Pharmacology Biochemistry and Behavior*, 100(1), 33-39.

Daza-Losada, M., Rodríguez-Arias, M., Aguilar, M. A., & Miñarro, J. (2009)b. Acquisition and reinstatement of MDMA-induced conditioned place preference

in mice pre-treated with MDMA or cocaine during adolescence. *Addiction Biology*, 14(4), 447-456.

Daza-Losada, M., Rodríguez-Arias, M., Maldonado, C., Aguilar, M. A., Guerri, C., & Miñarro, J. (2009)a. Acute behavioural and neurotoxic effects of MDMA plus cocaine in adolescent mice. *Neurotoxicology and Teratology*, 31(1), 49-59.

Daza-Losada, M., Rodríguez-Arias, M., Maldonado, C., Aguilar, M. A., & Miñarro, J. (2008). Behavioural and neurotoxic long-lasting effects of MDMA plus cocaine in adolescent mice. *European Journal of Pharmacology*, 590(1), 204-211.

de Fonseca, F. R., Ramos, J. A., Bonnin, A., & Fernández-Ruiz, J. J. (1993). Presence of cannabinoid binding sites in the brain from early postnatal ages. *Neuroreport*, 4(2), 135-138.

de Groot, J., van Milligen, F. J., Moonen-Leusen, B. W., Thomas, G., & Koolhaas, J. M. (1999). A single social defeat transiently suppresses the anti-viral immune response in mice. *Journal of Neuroimmunology*, 95(1), 143-151.

de la Monte S. M. & Kril J. J. (2014). Human alcohol-related neuropathology. *Acta Neuropathologica,* 127(1), 71-90.

De la torre, R., Farre, M., Roset, P. N., López, C. H., Mas, M., Ortuno, J., ... & Cami, J. (2000).Pharmacology of MDMA in humans. *Annals of the New York Academy of Sciences*, 914(1), 225-237.

De Olmos, J. S., & Heimer, L. (1999). The concepts of the ventral striatopallidal system and extended amygdala. *Annals of the New York Academy of Sciences*, 877(1), 1-32.

de Paula, V. F., Ribeiro, A., Pinheiro, M. L., Sakai, M., Lacava, M. C., Lapachinske, S. F., ... & Palermo-Neto, J. (2008). Methylenedioxymethamphetamine (Ecstasy) decreases neutrophil activity and alters leukocyte distribution in bone marrow, spleen and blood. *Neuroimmunomodulation*, 16(3), 191-200.

de Sousa Fernandes Perna, E. D. S. F., Theunissen, E. L., Kuypers, K. P. C., Heckman, P., de la Torre, R., Farre, M., & Ramaekers, J. G. (2014). Memory and

mood during MDMA intoxication, with and without memantine pretreatment. *Neuropharmacology*, 87, 198-205.

Degenhardt, L., Bruno, R., & Topp, L. (2010). Is ecstasy a drug of dependence?. *Drug and Alcohol Dependence*, 107(1), 1-10.

Demers, C. H., Bogdan, R., & Agrawal, A. (2014). The Genetics, Neurogenetics and Pharmacogenetics of Addiction. *Current Behavioral Neuroscience Reports*, 1(1), 33-44.

Dettling, A., Skopp, G., Graw, M., & Haffner, H. T. (2008). The influence of sex hormones on the elimination kinetics of ethanol. *Forensic Science International*, 177(2), 85-89.

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences*, 85(14), 5274-5278.

Di Ciano, P., & Everitt, B. J. (2005). Neuropsychopharmacology of drug seeking: Insights from studies with second-order schedules of drug reinforcement. *European Journal of Pharmacology*, 526(1), 186-198.

Dickerson, S. M., Walker, D. M., Reveron, M. E., Duvauchelle, C. L., & Gore, A. C. (2008). The recreational drug ecstasy disrupts the hypothalamic-pituitary-gonadal reproductive axis in adult male rats. *Neuroendocrinology*, 88(2), 95.

Diller A. J., Rocha A., Cardon A. L., Valles R., Wellman P. J., & Nation J. R. (2007). The effects of concurrent administration of +/-3,4-methylenedioxymethamphetamine and cocaine on conditioned place preference in the adult male rat. *Pharmacology Biochemistry & Behavior,* 88(2), 165-170.

Ding, Z. M., Ingraham, C. M., Rodd, Z. A., & McBride, W. J. (2014). The reinforcing effects of ethanol within the posterior ventral tegmental area depend on dopamine neurotransmission to forebrain cortico-limbic systems. *Addiction Biology*, in press.

Do Couto, B. R., Aguilar, M. A., Lluch, J., Rodríguez-Arias, M., & Miñarro, J. (2009). Social experiences affect reinstatement of cocaine-induced place preference in mice. *Psychopharmacology*, 207(3), 485-498.

Do Couto, B. R., Aguilar, M. A., Manzanedo, C., Rodriguez-Arias, M., Armario, A., & Minarro, J. (2006). Social stress is as effective as physical stress in reinstating morphine-induced place preference in mice. *Psychopharmacology*, 185(4), 459-470.

Do Couto, B. R., Rodríguez-Arias, M., Fuentes, S., Gagliano, H., Armario, A., Miñarro, J., & Aguilar, M. A. (2011). Adolescent pre-exposure to ethanol or MDMA prolongs the conditioned rewarding effects of MDMA. *Physiology & Behavior*, 103(5), 585-593.

Doblin, R., Greer, G., Holland, J., Jerome, L., Mithoefer, M. C., & Sessa, B. (2014). A reconsideration and response to Parrott AC (2013) "Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research". *Human Psychopharmacology: Clinical and Experimental*, 29(2), 105-108.

Docherty, J. R., & Green, A. R. (2010). The role of monoamines in the changes in body temperature induced by 3, 4-methylenedioxymethamphetamine (MDMA, ecstasy) and its derivatives. *British Journal of Pharmacology*, 160(5), 1029-1044.

Dodd, P. R., Beckmann, A. M., Davidson, M. S., & Wilce, P. A. (2000). Glutamate-mediated transmission, alcohol, and alcoholism. *Neurochemistry International*, 37(5), 509-533.

Doremus, T. L., Brunell, S. C., Varlinskaya, E. I., & Spear, L. P. (2003). Anxiogenic effects during withdrawal from acute ethanol in adolescent and adult rats. *Pharmacology Biochemistry and Behavior*, 75(2), 411-418.

Doremus-Fitzwater, T. L., Varlinskaya, E. I., & Spear, L. P. (2010). Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain and Cognition*, 72(1), 114-123.

Doyle, S. E., Ramôa, C., Garber, G., Newman, J., Toor, Z., & Lynch, W. J. (2014). A Shift in the Role of Glutamatergic Signaling in the Nucleus Accumbens Core

With the Development of an Addicted Phenotype. *Biological Psychiatry*, 76(10), 810-815.

Dumont, G. J. H., & Verkes, R. J. (2006). A review of acute effects of 3, 4-methylenedioxymethamphetamine in healthy volunteers. *Journal of Psychopharmacology*, 20(2), 176-187.

Eaton, D. K., Kann, L., Kinchen, S., Shanklin, S., Flint, K. H., Hawkins, J., ... & Wechsler, H. (2012). Youth risk behavior surveillance-United States, 2011. *Morbidity and Mortality Weekly Report Surveillance*, 61(4), 1-162.

Ehringer, M. A., Hoft, N. R., & Zunhammer, M. (2009). Reduced alcohol consumption in mice with access to a running wheel. *Alcohol*, 43(6), 443-452.

Ellenbroek, B. A., van der Kam, E. L., van der Elst, M. C., & Cools, A. R. (2005). Individual differences in drug dependence in rats: the role of genetic factors and life events. *European Journal of Pharmacology*, 526(1), 251-258.

Enoch, M. A. (2006). Genetic and environmental influences on the development of alcoholism. *Annals of the New York Academy of Sciences*, 1094(1), 193-201.

Erdozain A. M., **&** Callado L. F. (2014). Neurobiological alterations in alcohol addiction: a review. *Adicciones,* 26(4), 360-370.

Erdozain, A. M., & Callado, L. F. (2011). Involvement of the endocannabinoid system in alcohol dependence: the biochemical, behavioral and genetic evidence. *Drug and Alcohol Dependence*, 117(2), 102-110.

Ericson, M., Löf, E., Stomberg, R., & Söderpalm, B. (2009). The smoking cessation medication varenicline attenuates alcohol and nicotine interactions in the rat mesolimbic dopamine system. *Journal of Pharmacology and Experimental Therapeutics*, 329(1), 225-230.

Ernst, M., Daniele, T., & Frantz, K. (2011). New perspectives on adolescent motivated behavior: attention and conditioning. *Developmental Cognitive Neuroscience*, 1(4), 377-389.

Everitt, B. J. (2014). Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories–indications for novel treatments of addiction. *European Journal of Neuroscience*, 40(1), 2163-2182.

Everitt, B. J., & Robbins, T. W. (2000). Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behaviour. *Psychopharmacology*, 153(1), 17-30.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience*, 8(11), 1481-1489.

Everitt, B. J., & Robbins, T. W. (2013). From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neuroscience & Biobehavioral Reviews*, 37(9), 1946-1954.

Faisal, M., Waseem, D., Ismatullah, H., & Taqi, M. M. (2014). A molecular prospective provides new insights into implication of PDYN and OPRK1 genes in alcohol dependence. *Computers in Biology and Medicine*, 53, 250-257.

Fantegrossi, W. E., Ullrich, T., Rice, K. C., Woods, J. H., & Winger, G. (2002). 3, 4-Methylenedioxymethamphetamine (MDMA," ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. *Psychopharmacology*, 161(4), 356-364.

Federici, M., Nistico, R., Giustizieri, M., Bernardi, G., & Mercuri, N. B. (2009). Ethanol enhances GABAB-mediated inhibitory postsynaptic transmission on rat midbrain dopaminergic neurons by facilitating GIRK currents. *European Journal of Neuroscience*, 29(7), 1369-1377.

Feduccia, A. A., & Duvauchelle, C. L. (2008). Auditory stimuli enhance MDMA-conditioned reward and MDMA-induced nucleus accumbens dopamine, serotonin and locomotor responses. *Brain Research Bulletin*, 77(4), 189-196.

Feltenstein, M. W., & See, R. E. (2008). The neurocircuitry of addiction: an overview. *British Journal of Pharmacology*, 154(2), 261-274.

Ferraz-de-Paula, V., Stankevicius, D., Ribeiro, A., Pinheiro, M. L., Rodrigues-Costa, E. C., Florio, J. C., ... & Palermo-Neto, J. (2011). Differential behavioral outcomes of 3, 4-methylenedioxymethamphetamine (MDMA-ecstasy) in anxiety-like responses in mice. *Brazilian Journal of Medical and Biological Research*, 44(5), 428-437.

Ferreira, F. R., Oliveira, A. M., Dinarte, A. R., Pinheiro, D. G., Greene, L. J., Silva, W. A., ... & Guimarães, F. S. (2012). Changes in hippocampal gene expression by 7-nitroindazole in rats submitted to forced swimming stress. *Genes, Brain and Behavior*, 11(3), 303-313.

Field, M., Wiers, R. W., Christiansen, P., Fillmore, M. T., & Verster, J. C. (2010). Acute alcohol effects on inhibitory control and implicit cognition: implications for loss of control over drinking. *Alcoholism: Clinical and Experimental Research,* 34(8), 1346-1352.

Fields, H. L., Hjelmstad, G. O., Margolis, E. B., & Nicola, S. M. (2007). Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. *Annual Review* of *Neuroscience*, 30, 289-316.

Filbey, F. M., & DeWitt, S. J. (2012). Cannabis cue-elicited craving and the reward neurocircuitry. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 38(1), 30-35.

Finnegan, K. T., & Taraska, T. (1996). Effects of Glutamate Antagonists on Methamphetamine and 3, 4-Methylenedioxymethamphetamine-Induced Striatal Dopamine Release In Vivo. *Journal of Neurochemistry*, 66(5), 1949-1958.

Fisk, J. E., Murphy, P. N., Montgomery, C., & Hadjiefthyvoulou, F. (2011). Modelling the adverse effects associated with ecstasy use. *Addiction*, 106(4), 798-805.

Font L., Aragon C. M. & Miquel M. (2006). Ethanol-induced conditioned place preference, but not aversion, is blocked by treatment with D -penicillamine, an inactivation agent for acetaldehyde. *Psychopharmacology,* 184(1), 56-64.

Font, L., Miquel, M., & Aragon, C. M. (2008). Involvement of brain catalase activity in the acquisition of ethanol-induced conditioned place preference. *Physiology & Behavior*, 93(4), 733-741.

Fox, H., McLean, A., Turner, J., Parrott, A., Rogers, R., & Sahakian, B. (2002). Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology*, 162(2), 203-214.

Fox, M. E., Studebaker, R. I., Swofford, N. J., & Wightman, M. R. (2015). Stress and drug Dependence Differentially Modulate Norepinephrine Signaling in Animals with Varied HPA Axis Function. *Neuropsychopharmacology*, in press.

Freudenmann, R. W., Öxler, F., & Bernschneider-Reif, S. (2006). The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. *Addiction*, 101(9), 1241-1245.

Frick, K. M., & Gresack, J. E. (2003). Sex differences in the behavioral response to spatial and object novelty in adult C57BL/6 mice. *Behavioral Neuroscience*, 117(6), 1283.

Frith, C. H., Chang, L. W., Lattin, D. L., Walls, R. C., Hamm, J., & Doblin, R. (1987). Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat. *Toxicological Sciences*, 9(1), 110-119.

Funk, D., Vohra, S., & Le, A. D. (2004). Influence of stressors on the rewarding effects of alcohol in Wistar rats: studies with alcohol deprivation and place conditioning. *Psychopharmacology*, 176(1), 82-87.

Furay A. R., McDevitt R. A., Miczek K. A., & Neumaier J. F. (2011). 5-HT1B mRNA expression after chronic social stress. *Behavioural Brain Research*, 224(2), 350-357.

Gadek-Michalska A. & Bugajski J. (2008). Nitric oxide in the adrenergic-and CRH-induced activation of hypothalamic-pituitary-adrenal axis. *Physiology & Pharmacology*, 59(2), 365-378.

Galizio, M., Byrd, B. D., Robinson, A. M., Hawkey, A., Rayburn-Reeves, R., & April, L. B. (2014). Repeated Acquisition in the Morris Swim Task: Effects of Methylenedioxymethamphetamine, Methamphetamine, and Methylphenidate. *The Psychological Record*, 64(2), 143-150.

Galizio, M., McKinney, P., Cerutti, D. T., & Pitts, R. C. (2009). Effects of MDMA, methamphetamine and methylphenidate on repeated acquisition and performance in rats. *Pharmacology Biochemistry and Behavior*, 94(2), 305-311.

Gallagher, D. T., Hadjiefthyvoulou, F., Fisk, J. E., Montgomery, C., Robinson, S. J., & Judge, J. (2014). Prospective memory deficits in illicit polydrug users are associated with the average long-term typical dose of ecstasy typically consumed in a single session. *Neuropsychology*, 28(1), 43.

Gamsby, J. J., Templeton, E. L., Bonvini, L. A., Wang, W., Loros, J. J., Dunlap, J. C., ... & Gulick, D. (2013). The circadian Per1 and Per2 genes influence alcohol intake, reinforcement, and blood alcohol levels. *Behavioural Brain Research*, 249, 15-21.

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J. K., Sperry, L., Ross, T. J., ... & Stein, E. A. (2000). Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *American Journal of Psychiatry*, 157(11), 1789-1798.

García-Moreno, L. M., & Cimadevilla, J. M. (2012). Acute and chronic ethanol intake: effects on spatial and non-spatial memory in rats. *Alcohol*, 46(8), 757-762.

García-Pardo, M. P., Blanco-Gandía, M. C., Valiente-Lluch, M., Rodríguez-Arias, M., Miñarro, J., & Aguilar M. A. Long-term effects of repeated social stress on the conditioned place preference induced by MDMA in mice. Submitted.

García-Pardo, M. P., Escobar-Valero, C., Rodríguez-Arias, M., Miñarro, J & Aguilar M. A. Involvement of NMDA glutamate receptors in the acquisition and reinstatement of the conditioned place preference induced by MDMA. *Behavioural Pharmacology,* in press.

García-Pardo, M. P., Rodríguez-Arias, M., Maldonado, C., Manzanedo, C., Miñarro, J., & Aguilar, M. A. (2014). Effects of acute social stress on the conditioned place

preference induced by MDMA in adolescent and adult mice. *Behavioural Pharmacology,* 25(5-6), 532-546.

Gauvin, D. V., Briscoe, R. J., Goulden, K. L., & Holloway, F. A. (1994). Aversive attributes of ethanol can be attenuated by dyadic social interaction in the rat. *Alcohol*, 11(3), 247-251.

Gerra, G., Bassignana, S., Zaimovic, A., Moi, G., Bussandri, M., Caccavari, R., ... & Molina, E. (2003). Hypothalamic–pituitary–adrenal axis responses to stress in subjects with 3, 4-methylenedioxy-methamphetamine ('ecstasy') use history: correlation with dopamine receptor sensitivity. *Psychiatry Research*, 120(2), 115-124.

Gessa, G. L., Muntoni, F., Collu, M., Vargiu, L., & Mereu, G. (1985). Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. *Brain Research*, 348(1), 201-203.

Gianoulakis, C. (2009). Endogenous opioids and addiction to alcohol and other drugs of abuse. *Current Topics in Medicinal Chemistry*, 9(11), 999-1015.

Gilpin, N. W., Wright, M. J., Dickinson, G., Vandewater, S. A., Price, J. U., & Taffe, M. A. (2011). Influences of activity wheel access on the body temperature response to MDMA and methamphetamine. *Pharmacology Biochemistry and Behavior,* 99(3), 295-300.

Giuliano, C., Robbins, T. W., Nathan, P. J., Bullmore, E. T., & Everitt, B. J. (2012). Inhibition of opioid transmission at the μ-opioid receptor prevents both food seeking and binge-like eating. *Neuropsychopharmacology*, 37(12), 2643-2652.

Giuliano, C., Robbins, T. W., Wille, D. R., Bullmore, E. T., & Everitt, B. J. (2013). Attenuation of cocaine and heroin seeking by μ-opioid receptor antagonism. *Psychopharmacology*, 227(1), 137-147.

Givens, B. (1995). Low doses of ethanol impair spatial working memory and reduce hippocampal theta activity. *Alcoholism: Clinical and Experimental Research*, 19(3), 763-767.

Goeders, N. E. (2002). The HPA axis and cocaine reinforcement. *Psychoneuroendocrinology*, 27(1), 13-33.

Goeders, N. E. (2003). The impact of stress on addiction. *European Neuropsychopharmacology*, 13(6), 435-441.

Gonzales, R. A., & Weiss, F. (1998). Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. *The Journal of Neuroscience*, 18(24), 10663-10671.

Goodman, A. (2008). Neurobiology of addiction: An integrative review. *Biochemical Pharmacology*, 75(1), 266-322.

Gouzoulis-Mayfrank, E., & Daumann, J. (2009). Neurotoxicity of drugs of abuse-the case of methylenedioxy amphetamines (MDMA, ecstasy), and amphetamines. *Dialogues in Clinical Neuroscience*, 11(3), 305.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H. J., ... & Sass, H. (2000). Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *Journal of Neurology, Neurosurgery & Psychiatry*, 68(6), 719-725.

Grant, B. F., & Dawson, D. A. (1998). Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse*, 10(2), 163-173.

Green, A. R., Mechan, A. O., Elliott, J. M., O'Shea, E., & Colado, M. I. (2003). The pharmacology and clinical pharmacology of 3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacological Reviews*, 55(3), 463-508.

Green, A. S., & Grahame, N. J. (2008). Ethanol drinking in rodents: is free-choice drinking related to the reinforcing effects of ethanol?. *Alcohol*, 42(1), 1-11.

Greer, G., & Tolbert, R. (1986). Subjective reports of the effects of MDMA in a clinical setting. *Journal of Psychoactive Drugs*, 18(4), 319-327.

Gremel, C. M., & Cunningham, C. L. (2007). Role of test activity in ethanol-induced disruption of place preference expression in mice. *Psychopharmacology*, 191(2), 195-202.

Gremel, C. M., & Cunningham, C. L. (2008). Roles of the nucleus accumbens and amygdala in the acquisition and expression of ethanol-conditioned behavior in mice. *The Journal of Neuroscience*, 28(5), 1076-1084.

Griebel, G., Simiand, J., Serradeil-Le Gal, C., Wagnon, J., Pascal, M., Scatton, B., ... & Soubrié, P. (2002). Anxiolytic-and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proceedings of the National Academy of Sciences*, 99(9), 6370-6375.

Griffin III, W. C., McGovern, R. W., Bell, G. H., Randall, P. K., Middaugh, L. D., & Patrick, K. S. (2013). Interactive effects of methylphenidate and alcohol on discrimination, conditioned place preference and motor coordination in C57BL/6J mice. *Psychopharmacology*, 225(3), 613-625.

Grobin, A. C., Matthews, D. B., Devaud, L. L., & Morrow, A. L. (1998). The role of GABAA receptors in the acute and chronic effects of ethanol. *Psychopharmacology*, 139(1-2), 2-19.

Groblewski, P. A., Bax, L. S., & Cunningham, C. L. (2008). Reference-dose place conditioning with ethanol in mice: empirical and theoretical analysis. *Psychopharmacology*, 201(1), 97-106.

Groblewski, P. A., Lattal, K. M., & Cunningham, C. L. (2009). Effects of d-Cycloserine on Extinction and Reconditioning of Ethanol-Seeking Behavior in Mice. *Alcoholism: Clinical and Experimental Research*, 33(5), 772-782.

Gulick, D., & Gould, T. J. (2009)a. Interactive effects of ethanol and nicotine on learning, anxiety, and locomotion in C57BL/6 mice in the plus-maze discriminative avoidance task. *Neuropharmacology*, 57(3), 302-310.

Gulick, D., & Gould, T. J. (2009)b. Effects of ethanol and caffeine on behavior in C57BL/6 mice in the plus-maze discriminative avoidance task. *Behavioral Neuroscience*, 123(6), 1271.

Gulick, D., & Gould, T. J. (2009)c. The hippocampus and cingulate cortex differentially mediate the effects of nicotine on learning versus on ethanol-induced learning deficits through different effects at nicotinic receptors. *Neuropsychopharmacology*, 34(9), 2167-2179.

Gulick, D., & Gould, T. J. (2011). Nicotine acts in the anterior cingulate, but not dorsal or ventral hippocampus, to reverse ethanol-induced learning impairments in the plus-maze discriminative avoidance task. *Addiction Biology*, 16(1), 176-188.

Gulley, J. M., & Juraska, J. M. (2013). The effects of abused drugs on adolescent development of corticolimbic circuitry and behavior. *Neuroscience*, 249, 3-20.

Gurtman, C. G., Morley, K. C., Li, K. M., Hunt, G. E., & McGregor, I. S. (2002). Increased anxiety in rats after 3, 4-methylenedioxymethamphetamine: association with serotonin depletion. *European Journal of Pharmacology*, 446(1), 89-96.

Hall, A. P., & Henry, J. A. (2006). Acute toxic effects of 'Ecstasy'(MDMA) and related compounds: overview of pathophysiology and clinical management. *British Journal of Anaesthesia*, 96(6), 678-685.

Halpern, P., Moskovich, J., Avrahami, B., Bentur, Y., Soffer, D., & Peleg, K. (2011). Morbidity associated with MDMA (ecstasy) abuse-A survey of emergency department admissions. *Human & Experimental Toxicology*, 30(4), 259-66.

Halpin, L. E., Collins, S. A., & Yamamoto, B. K. (2014). Neurotoxicity of methamphetamine and 3, 4-methylenedioxymethamphetamine. *Life Sciences*, 97(1), 37-44.

Han, X., Albrechet-Souza, L., Doyle, M. R., Shimamoto, A., DeBold, J. F., & Miczek, K. A. (2015). Social stress and escalated drug self-administration in mice II. Cocaine and dopamine in the nucleus accumbens. *Psychopharmacology*, 32(6), 1003-10.

Harper, C., & Matsumoto, I. (2005). Ethanol and brain damage. *Current Opinion in Pharmacology*, 5(1), 73-78.

Harris, A. P., Holmes, M. C., De Kloet, E. R., Chapman, K. E., & Seckl, J. R. (2013). Mineralocorticoid and glucocorticoid receptor balance in control of HPA axis and behaviour. *Psychoneuroendocrinology*, 38(5), 648-658.

Harris, D. S., Baggott, M., Mendelson, J. H., Mendelson, J. E., & Jones, R. T. (2002). Subjective and hormonal effects of 3, 4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology*, 162(4), 396-405.

Heffernan, T. M., Ling, J., & Scholey, A. B. (2001). Subjective ratings of prospective memory deficits in MDMA ('ecstasy') users. *Human Psychopharmacology: Clinical and Experimental*, 16(4), 339-344.

Heilig, M., & Schank, J. R. (2014). Kappa-opioid receptor antagonism: a mechanism for treatment of relief drinking?. *Biological Psychiatry*, 75(10), 750-751.

Henderson-Redmond, A., & Czachowski, C. (2014). Effects of systemic opioid receptor ligands on ethanol-and sucrose seeking and drinking in alcohol-preferring (P) and Long Evans rats. *Psychopharmacology*, 231(22), 4309-4321.

Henry, J. A., Jeffreys, K. J., & Dawling, S. (1992). Toxicity and deaths from 3, 4-methylenedioxymethamphetamine (" ecstasy"). *The Lancet*, 340(8816), 384-387.

Herman, J. P., McKlveen, J. M., Solomon, M. B., Carvalho-Netto, E., & Myers, B. (2012). Neural regulation of the stress response: glucocorticoid feedback mechanisms. *Brazilian Journal of Medical and Biological Research*, 45(4), 292-298.

Hilbert, M. L., May, C. E., & Griffin, W. C. (2013). Conditioned reinforcement and locomotor activating effects of caffeine and ethanol combinations in mice. *Pharmacology Biochemistry and Behavior*, 110, 168-173.

Ho, Y. J., Pawlak, C. R., Guo, L., & Schwarting, R. K. (2004). Acute and long-term consequences of single MDMA administration in relation to individual anxiety levels in the rat. *Behavioural Brain Research*, 149(2), 135-144.

Hoffmann, J. P., Cerbone, F. G., & Su, S. S. (2000). A growth curve analysis of stress and adolescent drug use. *Substance Use & Misuse*, 35(5), 687-716.

Hoffmann, S. E., & Matthews, D. B. (2001). Ethanol-Induced Impairments in Spatial Working Memory Are Not Due to Deficits in Learning. *Alcoholism: Clinical and Experimental Research*, 25(6), 856-861.

Hosseinzadeh Asl N. R. & Hosseinalipour F. (2014). Effectiveness of mindfulness-based stress reduction intervention for health-related quality of life in drug-dependent males. *Iranian Red Crescent Medical Journal*, 16(9), e12608

Houchi, H., Warnault, V., Barbier, E., Dubois, C., Pierrefiche, O., Ledent, C., ... & Naassila, M. (2008). Involvement of A2A receptors in anxiolytic, locomotor and motivational properties of ethanol in mice. *Genes, Brain and Behavior*, 7(8), 887-898.

Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annual Review* of *Neuroscience*, 29, 565-598.

Hymel, K. A., Eans, S. O., Sitchenko, K. L., Gomes, S. M., Lukowsky, A. L., Medina, J. M., ... & McLaughlin, J. P. (2014). Stress-induced increases in depression-like and cocaine place-conditioned behaviors are reversed by disruption of memories during reconsolidation. *Behavioural Pharmacology*, 25(5 and 6), 599-608.

Hysek, C. M., Schmid, Y., Simmler, L. D., Domes, G., Heinrichs, M., Eisenegger, C., ... & Liechti, M. E. (2014). MDMA enhances emotional empathy and prosocial behavior. *Social Cognitive and Affective Neuroscience*, 9(11), 1645-1652.

Ikonomidou, C., Bittigau, P., Ishimaru, M. J., Wozniak, D. F., Koch, C., Genz, K., ... & Olney, J. W. (2000). Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science,* 287(5455), 1056-1060.

Itzhak, Y., & Martin, J. L. (2000). Blockade of alcohol-induced locomotor sensitization and conditioned place preference in DBA mice by 7-nitroindazole. *Brain Research*, 858(2), 402-407.

Itzhak, Y., Ali, S. F., Achat, C. N., & Anderson, K. L. (2003). Relevance of MDMA (" ecstasy")-induced neurotoxicity to long-lasting psychomotor stimulation in mice. *Psychopharmacology*, 166(3), 241-248.

Itzhak, Y., Martin, J. L., & Ali, S. F. (2000). Comparison between the Role of the Neuronal and Inducible Nitric Oxide Synthase in Methamphetamine-induced Neurotoxicity and Sensitization. *Annals of the New York Academy of Sciences*, 914(1), 104-111.

Itzhak, Y., Roger-Sánchez, C., & Anderson, K. L. (2009). Role of the nNOS gene in ethanol-induced conditioned place preference in mice. *Alcohol*, 43(4), 285-291.

Jacobson, L. (2014). Hypothalamic-Pituitary-Adrenocortical Axis: Neuropsychiatric Aspects. *Comprehensive Physiology*, 4(2), 715-738.

Jacobson-Pick, S., Audet, M. C., McQuaid, R. J., Kalvapalle, R., & Anisman, H. (2013). Social agonistic distress in male and female mice: changes of behavior and brain monoamine functioning in relation to acute and chronic challenges. *PloS One*, 8(4), e60133.

Jerlhag, E., Egecioglu, E., Landgren, S., Salomé, N., Heilig, M., Moechars, D., ... & Engel, J. A. (2009). Requirement of central ghrelin signaling for alcohol reward. *Proceedings of the National Academy of Sciences*, 106(27), 11318-11323.

Jin, H. M., Muna, S. S., Bagalkot, T. R., Cui, Y., Yadav, B. K., & Chung, Y. C. (2015). The Effects of Social Defeat on Behavior and Dopaminergic Markers in Mice. *Neuroscience*, 12(288), 167-77.

Johnson, B. N., & Yamamoto, B. K. (2009). Chronic unpredictable stress augments+ 3, 4-methylenedioxymethamphetamine-induced monoamine depletions: the role of corticosterone. *Neuroscience*, 159(4), 1233-1243.

Joung, H. Y., Jung, E. Y., Kim, K., Lee, M. S., Her, S., & Shim, I. (2012). The differential role of NOS inhibitors on stress-induced anxiety and neuroendocrine alterations in the rat. *Behavioural Brain Research*, 235(2), 176-181.

Jupp, B., & Dalley, J. W. (2014). Convergent pharmacological mechanisms in impulsivity and addiction: insights from rodent models. *British Journal of Pharmacology*, 171(20), 4729-4766.

Kabbaj, M., Norton, C., Kollack-Walker, S., Watson, S., Robinson, T., & Akil, H. (2001). Social defeat alters the acquisition of cocaine self-administration in rats: role of individual differences in cocaine-taking behavior. *Psychopharmacology*, 158(4), 382-387.

Kalant, H. (2001). The pharmacology and toxicology of "ecstasy"(MDMA) and related drugs. *Canadian Medical Association Journal*, 165(7), 917-928.

Kalechstein, A. D., De La Garza II, R., Mahoney III, J. J., Fantegrossi, W. E., & Newton, T. F. (2007). MDMA use and neurocognition: a meta-analytic review. *Psychopharmacology*, 189(4), 531-537.

Kameda, S. R., Frussa-Filho, R., Carvalho, R. C., Takatsu-Coleman, A. L., Ricardo, V. P., Patti, C. L., ... & Silva, R. H. (2007). Dissociation of the effects of ethanol on memory, anxiety, and motor behavior in mice tested in the plus-maze discriminative avoidance task. *Psychopharmacology*, 192(1), 39-48.

Kankaanpää, A., Meririnne, E., Lillsunde, P., & SeppÄlÄ, T. (1998). The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens. *Pharmacology Biochemistry and Behavior*, 59(4), 1003-1009.

Karkhanis, A. N., Locke, J. L., McCool, B. A., Weiner, J. L., & Jones, S. R. (2014). Social Isolation Rearing Increases Nucleus Accumbens Dopamine and Norepinephrine Responses to Acute Ethanol in Adulthood. *Alcoholism: Clinical and Experimental Research*, 38(11), 2770-2779.

Katner, S. N., Kerr, T. M., & Weiss, F. (1996). Ethanol anticipation enhances dopamine efflux in the nucleus accumbens of alcohol-preferring (P) but not Wistar rats. *Behavioural Pharmacology*, 7(7), 669-674.

Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nature reviews neuroscience*, 8(11), 844-858.

Ke, J. J., Chen, H. I., Jen, C. J., Kuo, Y. M., Cherng, C. G., Tsai, Y. P. N., ... & Yu, L. (2008). Mutual enhancement of central neurotoxicity induced by ketamine followed by methamphetamine. *Toxicology and Applied Pharmacology*, 227(2), 239-247.

Keeney, A. J., Hogg, S., & Marsden, C. A. (2001). Alterations in core body temperature, locomotor activity, and corticosterone following acute and repeated social defeat of male NMRI mice. *Physiology & Behavior*, 74(1), 177-184.

Kehr, J., Ichinose, F., Yoshitake, S., Goiny, M., Sievertsson, T., Nyberg, F., & Yoshitake, T. (2011). Mephedrone, compared with MDMA (ecstasy) and amphetamine, rapidly increases both dopamine and 5-HT levels in nucleus accumbens of awake rats. *British Journal of Pharmacology*, 164(8), 1949-1958.

Kelley, A. E., & Berridge, K. C. (2002). The neuroscience of natural rewards: relevance to addictive drugs. *The Journal of Neuroscience*, 22(9), 3306-3311.

King, K. M., & Chassin, L. (2008). Adolescent stressors, psychopathology, and young adult substance dependence: A prospective study. *Journal of Studies on Alcohol and Drugs*, 69(5), 629.

Kinsey, S. G., Bailey, M. T., Sheridan, J. F., Padgett, D. A., & Avitsur, R. (2007). Repeated social defeat causes increased anxiety-like behavior and alters splenocyte function in C57BL/6 and CD-1 mice. *Brain, Behavior, and Immunity*, 21(4), 458-466.

Kirkpatrick, M. G., Gunderson, E. W., Perez, A. Y., Haney, M., Foltin, R. W., & Hart, C. L. (2012). A direct comparison of the behavioral and physiological effects of methamphetamine and 3, 4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology*, 219(1), 109-122.

Kiyatkin, E. A., Kim, A. H., Wakabayashi, K. T., Baumann, M. H., & Shaham, Y. (2015). Effects of social interaction and warm ambient temperature on brain hyperthermia induced by the designer drugs methylone and MDPV. *Neuropsychopharmacology*, 40(2), 436-445.

Koob, G. F. (2009). Brain stress systems in the amygdala and addiction. *Brain Research*, 1293, 61-75.

Koob, G. F. (2010). The role of CRF and CRF-related peptides in the dark side of addiction. *Brain Research*, 1314, 3-14.

Koob, G. F. (2013). Addiction is a reward deficit and stress surfeit disorder. *Frontiers in Psychiatry*, 4, 72.

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, 24(2), 97-129.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, 35(1), 217-238.

Koob, G., & Kreek, M. D. (2007). Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *The American Journal of Psychiatry*, 164(8), 1149-1159.

Kopelman, M. D., Bright, P., Fulker, H., Hinton, N., Morrison, A., & Verfaellie, M. (2009). Remote semantic memory in patients with Korsakoff's syndrome and herpes encephalitis. *Neuropsychology*, 23(2), 144.

Kovács, K. J. (2013). CRH: the link between hormonal-, metabolic-and behavioral responses to stress. *Journal of Chemical Neuroanatomy*, 54, 25-33.

Krugers, H. J., Koolhaas, J. M., Bohus, B., & Korf, J. (1993). A single social stress-experience alters glutamate receptor-binding in rat hippocampal CA3 area. *Neuroscience Letters*, 154(1), 73-77.

Krystal, J. H., Petrakis, I. L., Limoncelli, D., Webb, E., Gueorgueva, R., D'Souza, D. C., ... & Charney, D. S. (2003). Altered NMDA glutamate receptor antagonist response in recovering ethanol-dependent patients. *Neuropsychopharmacology*, 28(11), 2020-2028.

Krystal, J. H., Price, L. H., Opsahl, C., Ricaurte, G. A., & Heninger, G. R. (1992). Chronic 3, 4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function?. *The American Journal of Drug and Alcohol Abuse*, 18(3), 331-341.

Kupfermann, I. (1991). Hypothalamus and limbic system: peptidergic neurons, homeostasis, and emotional behavior. *Principles of Neural Science*, 3, 735-749.

Kurosaki, R., Muramatsu, Y., Michimata, M., Matsubara, M., Kato, H., Imai, Y., ... & Araki, T. (2002). Role of nitric oxide synthase against MPTP neurotoxicity in mice. *Neurological Research*, 24(7), 655-662.

Kuypers, K. P., Wingen, M., Samyn, N., Limbert, N., & Ramaekers, J. G. (2007). Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night. *Psychopharmacology*, 192(1), 111-119.

Lamers, C. T., Ramaekers, J. G., Muntjewerff, N. D., Sikkema, K. L., Riedel, W. J., Samyn, N., ... & Brookhuis, K. A. (2003). Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance. *Journal of Psychopharmacology*, 17(4), 379-387.

Laviola, G., Macrì, S., Morley-Fletcher, S., & Adriani, W. (2003). Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. *Neuroscience & Biobehavioral Reviews*, 27(1), 19-31.

Laviola, G., Pascucci, T., & Pieretti, S. (2001). Striatal dopamine sensitization to D-amphetamine in periadolescent but not in adult rats. *Pharmacology Biochemistry and Behavior*, 68(1), 115-124.

Le Moal, M. (2009). Drug abuse: vulnerability and transition to addiction. *Pharmacopsychiatry*, 42 (S1), S42-55.

Ledesma, J. C., & Aragon, C. M. (2013). Acquisition and reconditioning of ethanol-induced conditioned place preference in mice is blocked by the H2O2 scavenger alpha lipoic acid. *Psychopharmacology,* 226(4), 673-685.

Lessem, J. M., Hopfer, C. J., Haberstick, B. C., Timberlake, D., Ehringer, M. A., Smolen, A., & Hewitt, J. K. (2006). Relationship between adolescent marijuana use and young adult illicit drug use. *Behavior Genetics*, 36(4), 498-506.

Leung, K. S., Abdallah, A. B., Copeland, J., & Cottler, L. B. (2010). Modifiable risk factors of ecstasy use: Risk perception, current dependence, perceived control, and depression. *Addictive Behaviors*, 35(3), 201-208.

Lew, R., Sabol, K. E., Chou, C., Vosmer, G. L., Richards, J., & Seiden, L. S. (1996). Methylenedioxymethamphetamine-induced serotonin deficits are followed by partial recovery over a 52-week period. Part II: Radioligand binding and autoradiography studies. *Journal of Pharmacology and Experimental Therapeutics*, 276(2), 855-865.

Leyton, M., & Vezina, P. (2014). Dopamine ups and downs in vulnerability to addictions: a neurodevelopmental model. *Trends in Pharmacological Sciences*, 35(6), 268-276.

Li, S. M., Ren, Y. H., & Zheng, J. W. (2002)a. Effect of 7-nitroindazole on drug-priming reinstatement of D-methamphetamine-induced conditioned place preference. *European Journal of Pharmacology*, 443(1), 205-206.

Li, S. M., Yin, L. L., Shi, J., Lin, Z. B., & Zheng, J. W. (2002)b. The effect of 7-nitroindazole on the acquisition and expression of D-methamphetamine-induced place preference in rats. *European Journal of Pharmacology*, 435(2), 217-223.

Liddie, S., A Balda, M., & Itzhak, Y. (2013). Nitric Oxide (NO) Signaling as a Potential Therapeutic Modality Against Psychostimulants. *Current Pharmaceutical Design*, 19(40), 7092-7102.

Liechti, M. (2015). Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signalling. *Swiss Medical Weekly*, 145, w14043.

Liechti, M. E., & Vollenweider, F. X. (2001). Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Human Psychopharmacology: Clinical and Experimental*, 16(8), 589-598.

Liechti, M. E., Baumann, C., Gamma, A., & Vollenweider, F. X. (2000)b. Acute psychological effects of 3, 4-methylenedioxymethamphetamine (MDMA,"Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology*, 22(5), 513-521.

Liechti, M. E., Saur, M. R., Gamma, A., Hell, D., & Vollenweider, F. X. (2000)a. Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT2 antagonist ketanserin in healthy humans. *Neuropsychopharmacology*, 23(4), 396-404.

Lile, J. A., Ross, J. T., & Nader, M. A. (2005). A comparison of the reinforcing efficacy of 3, 4-methylenedioxymethamphetamine (MDMA,"ecstasy") with cocaine in rhesus monkeys. *Drug and Alcohol Dependence*, 78(2), 135-140.

Linsenbardt, D. N., & Boehm, S. L. (2009). Agonism of the endocannabinoid system modulates binge-like alcohol intake in male C57BL/6J mice: involvement of the posterior ventral tegmental area. *Neuroscience*, 164(2), 424-434.

Lizarraga, L. E., Cholanians, A. B., Phan, A. V., Herndon, J. M., Lau, S. S., & Monks, T. J. (2015). Vesicular Monoamine Transporter 2 and the Acute and Long-Term Response to 3, 4-(±)-Methylenedioxymethamphetamine. *Toxicological Sciences*, 143(1), 209-219.

Llorente-Berzal, A., Manzanedo, C., Daza-Losada, M., Valero, M., López-Gallardo, M., Aguilar, M. A.,& Viveros, M. P. (2013). Sex-dependent effects of early maternal deprivation on MDMA-induced conditioned place preference in adolescent rats: possible neurochemical correlates. *Toxicology*, 311(1), 78-86.

Logrip M. L., Koob G. F., & Zorrilla E. P. (2011). Role of corticotropin-releasing factor in drug addiction: potential for pharmacological intervention. *Central Nervous System Drugs,* 25(4),271-87

Logrip, M. L., Zorrilla, E. P., & Koob, G. F. (2012). Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder. *Neuropharmacology*, 62(2), 552-564.

Lopez, M. F., & Laber, K. (2014). Impact of social isolation and enriched environment during adolescence on voluntary ethanol intake and anxiety in C57BL/6J mice. *Physiology & Behavior*, in press.

Lopez-Rodriguez, A. B., Llorente-Berzal, A., Garcia-Segura, L. M., & Viveros, M. P. (2014). Sex-dependent long-term effects of adolescent exposure to THC and/or

MDMA on neuroinflammation and serotoninergic and cannabinoid systems in rats. *British Journal of Pharmacology*, 171(6), 1435-1447.

Lüscher, C., & Malenka, R. C. (2011). Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron*, 69(4), 650-663.

Lukas, M., Toth, I., Reber, S. O., Slattery, D. A., Veenema, A. H., & Neumann, I. D. (2011). The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice. *Neuropsychopharmacology*, 36(11), 2159-2168.

Lumley, L. A., Sipos, M. L., Charles, R. C., Charles, R. F., & Meyerhoff, J. L. (1999). Social stress effects on territorial marking and ultrasonic vocalizations in mice. *Physiology & Behavior*, 67(5), 769-775.

Machalova, A., Slais, K., Vrskova, D., & Sulcova, A. (2012). Differential effects of modafinil, methamphetamine, and MDMA on agonistic behavior in male mice. *Pharmacology Biochemistry and Behavior*, 102(2), 215-223.

Maldonado, C., Rodriguez-Arias, M., Castillo, A., Aguilar, M. A., & Minarro, J. (2007). Effect of memantine and CNQX in the acquisition, expression and reinstatement of cocaine-induced conditioned place preference. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 31(4), 932-939.

Maldonado, R., Valverde, O., & Berrendero, F. (2006). Involvement of the endocannabinoid system in drug addiction. *Trends in Neurosciences*, 29(4), 225-232.

Manzanedo, C., Aguilar, M. A., Do Couto, B. R., Rodríguez-Arias, M., & Miñarro, J. (2009). Involvement of nitric oxide synthesis in sensitization to the rewarding effects of morphine. *Neuroscience Letters*, 464(1), 67-70.

Manzanedo, C., Aguilar, M. A., Rodríguez-Arias, M., & Miñarro, J. (2001). Effects of dopamine antagonists with different receptor blockade profiles on morphine-induced place preference in male mice. *Behavioural Brain Research*, 121(1), 189-197.

Manzanedo, C., Aguilar, M. A., Rodríguez-Arias, M., Navarro, M., & Miñarro, J. (2004). 7-Nitroindazole blocks conditioned place preference but not hyperactivity induced by morphine. *Behavioural Brain Research*, 150(1), 73-82.

Manzanedo, C., Rodríguez-Arias, M., Daza-Losada, M., Maldonado, C., Aguilar, M. A., & Miñarro, J. (2010). Effect of the CB1 cannabinoid agonist WIN 55212-2 on the acquisition and reinstatement of MDMA-induced conditioned place preference in mice. *Behav Brain Funct*, 6(19), 1-11.

Marinelli, P. W., Lam, M., Bai, L., Quirion, R., & Gianoulakis, C. (2006). A microdialysis profile of dynorphin A1–8 release in the rat nucleus accumbens following alcohol administration. *Alcoholism: Clinical and Experimental Research*, 30(6), 982-990.

Marona-Lewicka, D., Rhee, G. S., Sprague, J. E., & Nichols, D. E. (1996). Reinforcing effects of certain serotonin-releasing amphetamine derivatives. *Pharmacology Biochemistry and Behavior*, 53(1), 99-105.

Marston, H. M., Reid, M. E., Lawrence, J. A., Olverman, H. J., & Butcher, S. P. (1999). Behavioural analysis of the acute and chronic effects of MDMA treatment in the rat. *Psychopharmacology*, 144(1), 67-76.

Martin, J. L., & Itzhak, Y. (2000). 7-Nitroindazole blocks nicotine-induced conditioned place preference but not LiCl-induced conditioned place aversion. *Neuroreport*, 11(5), 947-949.

Marty, V. N., & Spigelman, I. (2012). Long-Lasting Alterations in Membrane Properties, K+ Currents, and Glutamatergic Synaptic Currents of Nucleus Accumbens Medium Spiny Neurons in a Rat Model of Alcohol Dependence. *Frontiers in Neuroscience*, 6, 86.

Mateos-García, A., Roger-Sánchez, C., Rodriguez-Arias, M., Miñarro, J., Aguilar, M. A., Manzanedo, C., & Arenas, M. C. (2015). Higher sensitivity to the conditioned rewarding effects of cocaine and MDMA in High-Novelty-Seekers mice exposed to a cocaine binge during adolescence. *Psychopharmacology*, 232(1), 101-113.

Matthews, D. B., Tinsley, K. L., Diaz-Granados, J. L., Tokunaga, S., & Silvers, J. M. (2008). Chronic intermittent exposure to ethanol during adolescence produces

tolerance to the hypnotic effects of ethanol in male rats: a dose-dependent analysis. *Alcohol*, 42(8), 617-621.

McAleer, L. M., Schallert, T., & Duvauchelle, C. L. (2013). Weekend Ecstasy use disrupts memory in rats. *Neuroscience Letters*, 549, 173-176.

McBride, W. J., Murphy, J. M., & Ikemoto, S. (1999). Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. *Behavioural Brain Research*, 101(2), 129-152.

McCann U. D., Szabo Z., Seckin E., Rosenblatt P., Mathews W. B., Ravert H. T., Dannals R. F. & Ricaurte G. A. (2005) Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. *Neuropsychopharmacology,* 30(9), 1741-50.

McCann, U. D., Mertl, M., Eligulashvili, V., & Ricaurte, G. A. (1999). Cognitive performance in (±) 3, 4-methylenedioxymethamphetamine (MDMA,"ecstasy") users: a controlled study. *Psychopharmacology*, 143(4), 417-425.

McCann, U. D., Szabo, Z., Scheffel, U., Dannals, R. F., & Ricaurte, G. A. (1998). Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *The Lancet*, 352(9138), 1433-1437.

McClain, J. A., Morris, S. A., Marshall, S. A., & Nixon, K. (2014). Ectopic hippocampal neurogenesis in adolescent male rats following alcohol dependence. *Addiction Biology*, 19(4), 687-699.

McCormick, C. M. (2010). An animal model of social instability stress in adolescence and risk for drugs of abuse. *Physiology & Behavior*, 99(2), 194-203.

McEwen, B. S. (2003). Mood disorders and allostatic load. *Biological Psychiatry*, 54(3), 200-207.

McEwen, B. S., & Morrison, J. H. (2013). The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron*, 79(1), 16-29.

McGregor, I. S., Gurtman, C. G., Morley, K. C., Clemens, K. J., Blokland, A., Li, K. M., ... & Hunt, G. E. (2003). Increased anxiety and" depressive" symptoms months

after MDMA (" ecstasy") in rats: drug-induced hyperthermia does not predict long-term outcomes. *Psychopharmacology*, 168(4), 465-474.

McLaughlin, J. P., Li, S., Valdez, J., Chavkin, T. A., & Chavkin, C. (2006). Social defeat stress-induced behavioral responses are mediated by the endogenous kappa opioid system. *Neuropsychopharmacology*, 31(6), 1241-1248.

McMullen, P. A., Saint-Cyr, J. A., & Carlen, P. L. (1984). Morphological alterations in rat CA1 hippocampal pyramidal cell dendrites resulting from chronic ethanol consumption and withdrawal. *Journal of Comparative Neurology*, 225(1), 111-118.

Meerlo, P., Overkamp, G. J. F., Daan, S., Van Den Hoofdakker, R. H., & Koolhaas, J. M. (1996). Changes in behaviour and body weight following a single or double social defeat in rats. *Stress: The International Journal on the Biology of Stress*, 1(1), 21-32.

Meyer, A., Mayerhofer, A., Kovar, K. A., & Schmidt, W. J. (2002). Rewarding effects of the optical isomers of 3, 4-methylenedioxy-methylamphetamine ('Ecstasy') and 3, 4-methylenedioxy-ethylamphetamine ('Eve') measured by conditioned place preference in rats. *Neuroscience Letters*, 330(3), 280-284.

Meyer, J. S. (2013). 3, 4-methylenedioxymethamphetamine (MDMA): current perspectives. *Substance Abuse and Rehabilitation*, 4, 83-99.

Michael White, C. (2014). How MDMA's pharmacology and pharmacokinetics drive desired effects and harms. *The Journal of Clinical Pharmacology*, 54(3), 245-252.

Miczek, K. A., Nikulina, E. M., Shimamoto, A., & Covington, H. E. (2011). Escalated or suppressed cocaine reward, tegmental BDNF, and accumbal dopamine caused by episodic versus continuous social stress in rats. *The Journal of Neuroscience*, 31(27), 9848-9857.

Miczek, K. A., Thompson, M. L., & Shuster, L. (1982). Opioid-like analgesia in defeated mice. *Science*, 215(4539), 1520-1522.

Miczek, K. A., Yap, J. J., & Covington, H. E. (2008). Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. *Pharmacology & Therapeutics*, 120(2), 102-128.

Miguel-Hidalgo, J. J., & Rajkowska, G. (2003). Comparison of prefrontal cell pathology between depression and alcohol dependence. *Journal of Psychiatric Research*, 37(5), 411-420.

Miguel-Hidalgo, J. J., Overholser, J. C., Meltzer, H. Y., Stockmeier, C. A., & Rajkowska, G. (2006). Reduced glial and neuronal packing density in the orbitofrontal cortex in alcohol dependence and its relationship with suicide and duration of alcohol dependence. *Alcoholism: Clinical and Experimental Research*, 30(11), 1845-1855.

Miller, D. B., & O'Callaghan, J. P. (2002). Neuroendocrine aspects of the response to stress. *Metabolism*, 51(6), 5-10.

Mokler, D. J., Robinson, S. E., & Rosecrans, J. A. (1987). (±) 3, 4-Methylenedioxymethamphetamine (MDMA) produces long-term reductions in brain 5-hydroxytryptamine in rats. *European Journal of Pharmacology*, 138(2), 265-268.

Montagud-Romero, S., Daza-Losada, M., Vidal-Infer, A., Maldonado, C., Aguilar, M. A., Miñarro, J., & Rodríguez-Arias, M. (2014). The Novelty-Seeking Phenotype Modulates the Long-Lasting Effects of Intermittent Ethanol Administration during Adolescence. *PloS One*, 9(3), e92576.

Montesinos, J., Pascual, M., Pla, A., Maldonado, C., Rodríguez-Arias, M., Miñarro, J., & Guerri, C. (2015). TLR4 elimination prevents synaptic and myelin alterations and long-term cognitive dysfunctions in adolescent mice with intermittent ethanol treatment. *Brain, Behavior and Immunity*, 45, 233-244.

Moore, E. M., Migliorini, R., Infante, M. A., & Riley, E. P. (2014). Fetal Alcohol Spectrum Disorders: Recent Neuroimaging Findings. *Current Developmental Disorders Reports*, 1(3), 161-172.

Morgan, C. J., Noronha, L. A., Muetzelfeldt, M., Fielding, A., & Curran, H. V. (2013). Harms and benefits associated with psychoactive drugs: findings of an

international survey of active drug users. *Journal of Psychopharmacology*, 27(6), 497-506.

Morgan, M. J. (1999). Memory deficits associated with recreational use of "ecstasy"(MDMA). *Psychopharmacology*, 141(1), 30-36.

Morimoto, B. H., Lovell, S., & Kahr, B. (1998). Ecstasy: 3, 4-methylenedioxymethamphetamine (MDMA). *Acta Crystallographica Section C: Crystal Structure Communications*, 54(2), 229-231.

Morley, K. C., Gallate, J. E., Hunt, G. E., Mallet, P. E., & McGregor, I. S. (2001). Increased anxiety and impaired memory in rats 3 months after administration of 3, 4-methylenedioxymethamphetamine ("ecstasy"). *European Journal of Pharmacology*, 433(1), 91-99.

Moyano, S., Frechilla, D., & Del Rio, J. (2004). NMDA receptor subunit and CaMKII changes in rat hippocampus induced by acute MDMA treatment: a mechanism for learning impairment. *Psychopharmacology*, 173(3-4), 337-345.

Mrejeru, A., Martí-Prats, L., Avegno, E. M., Harrison, N. L., & Sulzer, D. (2015). A subset of ventral tegmental area dopamine neurons responds to acute ethanol. *Neuroscience*, 290, 649-658.

Müller, C. P., & Homberg, J. R. (2015). The role of serotonin in drug use and addiction. *Behavioural Brain Research*, 277, 146-192.

Mueller, M., Maldonado-Adrian, C., Yuan, J., McCann, U. D., & Ricaurte, G. A. (2013). Studies of (±)-3, 4-methylenedioxymethamphetamine (MDMA) metabolism and disposition in rats and mice: relationship to neuroprotection and neurotoxicity profile. *Journal of Pharmacology and Experimental Therapeutics*, 344(2), 479-488.

Mueller, M., Peters, F. T., Maurer, H. H., McCann, U. D., & Ricaurte, G. A. (2008). Nonlinear pharmacokinetics of (±) 3, 4-methylenedioxymethamphetamine (MDMA,"Ecstasy") and its major metabolites in squirrel monkeys at plasma concentrations of MDMA that develop after typical psychoactive doses. *Journal of Pharmacology and Experimental Therapeutics*, 327(1), 38-44.

Mueller, M., Yuan, J., Maldonado Adrian, C., Mccann, U. D., & Ricaurte, G. A. (2011). Inhibition of 3, 4-methylenedioxymethamphetamine metabolism leads to marked decrease in 3, 4-dihydroxymethamphetamine formation but no change in serotonin neurotoxicity: Implications for mechanisms of neurotoxicity. *Synapse*, 65(10), 983-990.

Nathan, P. J., O'Neill, B. V., Bush, M. A., Koch, A., Tao, W. X., Maltby, K., ... & Bullmore, E. T. (2012). Opioid Receptor Modulation of Hedonic Taste Preference and Food Intake: A Single-Dose Safety, Pharmacokinetic, and Pharmacodynamic Investigation With GSK1521498, a Novel μ-Opioid Receptor Inverse Agonist. *The Journal of Clinical Pharmacology*, 52(4), 464-474.

Neisewander, J. L., Peartree, N. A., & Pentkowski, N. S. (2012). Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction. *Psychopharmacology*, 224(1), 33-56.

Nestler, E. J., & Carlezon, W. A. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry*, 59(12), 1151-1159.

Newton, P. M., Zeng, L., Wang, V., Connolly, J., Wallace, M. J., Kim, C., ... & Messing, R. O. (2008). A blocker of N-and T-type voltage-gated calcium channels attenuates ethanol-induced intoxication, place preference, self-administration, and reinstatement. *The Journal of Neuroscience*, 28(45), 11712-11719.

Nichols, D. E. (1986). Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *Journal of Psychoactive Drugs*, 18(4), 305-313.

Nichols, D. E., & Oberlender, R. (1989). Structure-activity relationships of MDMA-like substances. *NIDA Research Monograph*, 94, 1-29.

Nieoullon, A. (2002). Dopamine and the regulation of cognition and attention. *Progress in Neurobiology*, *67*(1), 53-83.

Nisijima, K., Kuboshima, K., Shioda, K., Yoshino, T., Iwamura, T., & Kato, S. (2012). Memantine attenuates 3, 4-methylenedioxymethamphetamine-induced hyperthermia in rats. *Neuroscience Letters*, 531(2), 198-203.

Norman, K. J., Seiden, J. A., Klickstein, J. A., Han, X., Hwa, L. S., DeBold, J. F., & Miczek, K. A. (2015). Social stress and escalated drug self-administration in mice I. Alcohol and corticosterone. *Psychopharmacology*, 232(6), 991-1001.

Nutt, D. J. (2014). The role of the opioid system in alcohol dependence. *Journal of Psychopharmacology*, 28(1), 8-22.

Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: a multicriteria decision analysis. *The Lancet*, 376(9752), 1558-1565.

O´Shea, E., Granados, R., Esteban, B., Colado, M. I., & Green, A. R. (1998). The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA (ecstasy'). *Neuropharmacology*, 37(7), 919-926.

O'Banion, M. K. (1999). COX-2 and Alzheimer's disease: potential roles in inflammation and neurodegeneration. *Expert Opinion on Investigational Drugs*, 8(10), 1521-1536.

Oberlin, B. G., Dzemidzic, M., Tran, S. M., Soeurt, C. M., Albrecht, D. S., Yoder, K. K., & Kareken, D. A. (2013). Beer flavor provokes striatal dopamine release in male drinkers: mediation by family history of alcoholism. *Neuropsychopharmacology*, 38(9), 1617-1624.

O'Brien, C. P., Childress, A. R., Ehrman, R., & Robbins, S. J. (1998). Conditioning factors in drug abuse: can they explain compulsion?. *Journal of Psychopharmacology*, 12(1), 15-22.

O'Cain, P. A., Hletko, S. B., Ogden, B. A., & Varner, K. J. (2000). Cardiovascular and sympathetic responses and reflex changes elicited by MDMA. *Physiology & Behavior*, 70(1), 141-148.

O'Hearn E., Battaglia G., De Souza E. B., Kuhar M. J., & Molliver M. E. Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: immunocytochemical evidence for neurotoxicity. (1988). *Neurocience,* 8(8), 2788-2803.

Olive, M. F., Cleva, R. M., Kalivas, P. W., & Malcolm, R. J. (2012). Glutamatergic medications for the treatment of drug and behavioral addictions. *Pharmacology Biochemistry and Behavior*, 100(4), 801-810.

Olive, M. F., Koenig, H. N., Nannini, M. A., & Hodge, C. W. (2001). Stimulation of endorphin neurotransmission in the nucleus accumbens by ethanol, cocaine, and amphetamine. *Journal of Neuroscience*, 21(23), RC184.

Orejarena, M. J., Berrendero, F., Maldonado, R., & Robledo, P. (2009). Differential changes in mesolimbic dopamine following contingent and non-contingent MDMA self-administration in mice. *Psychopharmacology*, 205(3), 457-466.

Orejarena, M. J., Lanfumey, L., Maldonado, R., & Robledo, P. (2011). Involvement of 5-HT2A receptors in MDMA reinforcement and cue-induced reinstatement of MDMA-seeking behaviour. *International Journal of Neuropsychopharmacology*, 14(7), 927-940.

O'Shea, E., Escobedo, I., Orio, L., Sanchez, V., Navarro, M., Green, A. R., & Colado, M. I. (2005). Elevation of ambient room temperature has differential effects on MDMA-induced 5-HT and dopamine release in striatum and nucleus accumbens of rats. *Neuropsychopharmacology*, 30(7), 1312-1323.

Pandey, S. C., Ugale, R., Zhang, H., Tang, L., & Prakash, A. (2008). Brain chromatin remodeling: a novel mechanism of alcoholism. *The Journal of Neuroscience*, 28(14), 3729-3737.

Parolaro, D., & Rubino, T. (2008). The role of the endogenous cannabinoid system in drug addiction. *Drug News & Perspectives*, 21(3), 149-57.

Parrott, A. C. (2001). Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology: Clinical and Experimental*, 16(8), 557-577.

Parrott, A. C. (2002). Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology Biochemistry and Behavior*, 71(4), 837-844.

Parrott, A. C. (2012)a. MDMA and 5-HT neurotoxicity: the empirical evidence for its adverse effects in humans–no need for translation. *British Journal of Pharmacology*, 166(5), 1518-1520.

Parrott, A. C. (2012)b. MDMA and temperature: a review of the thermal effects of 'Ecstasy'in humans. *Drug and Alcohol Dependence*, 121(1), 1-9.

Parrott, A. C. (2013)a. Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research. *Human Psychopharmacology: Clinical and Experimental*, 28(4), 289-307.

Parrott, A. C. (2013)b. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational 'Ecstasy'users. *Neuroscience & Biobehavioral Reviews*, 37(8), 1466-1484.

Parrott, A. C. (2014)a. The potential dangers of using MDMA for psychotherapy. *Journal of Psychoactive Drugs*, 46(1), 37-43.

Parrott, A. C. (2014)b. MDMA is certainly damaging after 25 years of empirical research: a reply and refutation of Doblin et al.(2014). *Human Psychopharmacology: Clinical and Experimental*, 29(2), 109-119.

Parrott, A. C., & Lasky, J. (1998). Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology*, 139(3), 261-268.

Parrott, A. C., Gibbs, A., Scholey, A. B., King, R., Owens, K., Swann, P., ... & Stough, C. (2011). MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study. *Psychopharmacology*, 215(3), 527-536.

Parrott, A. C., Lock, J., Conner, A. C., Kissling, C., & Thome, J. (2008). Dance clubbing on MDMA and during abstinence from Ecstasy/MDMA: prospective neuroendocrine and psychobiological changes. *Neuropsychobiology*, 57(4), 165.

Parrott, A. C., Montgomery, C., Wetherell, M. A., Downey, L. A., Stough, C., & Scholey, A. B. (2014)c. MDMA, cortisol, and heightened stress in recreational ecstasy users. *Behavioural Pharmacology*, 25(5 and 6), 458-472.

Parrott, A. C., Rodgers, J., Buchanan, T., Ling, J., Heffernan, T., & Scholey, A. B. (2006). Dancing hot on Ecstasy: physical activity and thermal comfort ratings are associated with the memory and other psychobiological problems reported by recreational MDMA users. *Human Psychopharmacology: Clinical and Experimental*, 21(5), 285-298.

Pascual, M., Baliño, P., Alfonso-Loeches, S., Aragón, C. M., & Guerri, C. (2011). Impact of TLR4 on behavioral and cognitive dysfunctions associated with alcohol-induced neuroinflammatory damage. *Brain, Behavior, and Immunity*, 25, S80-S91.

Pascual, M., Blanco, A. M., Cauli, O., Minarro, J., & Guerri, C. (2007). Intermittent ethanol exposure induces inflammatory brain damage and causes long-term behavioural alterations in adolescent rats. *European Journal of Neuroscience*, 25(2), 541-550.

Pascual, M., Pla, A., Miñarro, J., & Guerri, C. (2014). Neuroimmune activation and myelin changes in adolescent rats exposed to high-dose alcohol and associated cognitive dysfunction: a review with reference to human adolescent drinking. *Alcohol and Alcoholism*, 49(2), 187-192.

Pava, M. J., & Woodward, J. J. (2012). A review of the interactions between alcohol and the endocannabinoid system: implications for alcohol dependence and future directions for research. *Alcohol*, 46(3), 185-204.

Pentney, A. R. (2001). An exploration of the history and controversies surrounding MDMA and MDA. *Journal of Psychoactive Drugs*, 33(3), 213-221.

Pickles, A., Pickering, K., Simonoff, E., Silberg, J., Meyer, J., & Maes, H. (1998). Genetic clocks and soft events: A twin model for pubertal development and other recalled sequences of developmental milestones, transitions, or ages at onset. *Behavior Genetics*, 28(4), 243–253.

Pierce, R. C., & Wolf, M. E. (2013). Psychostimulant-induced neuroadaptations in nucleus accumbens AMPA receptor transmission. *Cold Spring Harbor Perspectives in Medicine*, 3(2), a012021.

Pina, M. M., & Cunningham, C. L. (2014). Effects of dopamine receptor antagonists on the acquisition of ethanol-induced conditioned place preference in mice. *Psychopharmacology*, 231(3), 459-468.

Piper, B. J., Fraiman, J. B., & Meyer, J. S. (2005). Repeated MDMA ("Ecstasy") exposure in adolescent male rats alters temperature regulation, spontaneous motor activity, attention, and serotonin transporter binding. *Developmental Psychobiology*, 47(2), 145-157.

Plaza-Zabala A., Berrendero F., Suarez J., Bermudez-Silva F. J., Fernandez-Espejo E., Serrano A., Pavon F. J., Parsons L. H., De Fonseca F. R., Maldonado R., Robledo P. Effects of the endogenous PPAR-alpha agonist, oleoylethanolamide on MDMA-induced cognitive deficits in mice. (2010). *Synapse,* 64(5), 379-389.

Plescia, F., Brancato, A., Venniro, M., Maniaci, G., Cannizzaro, E., Sutera, F. M., ... & Cannizzaro, C. (2015). Acetaldehyde self-administration by a two-bottle choice paradigm: consequences on emotional reactivity, spatial learning, and memory. *Alcohol*, 49(2), 139-148.

Pohorecky, L. A., & Brick, J. (1988). Pharmacology of ethanol. *Pharmacology & Therapeutics*, 36(2), 335-427.

Polter, A. M., & Kauer, J. A. (2014). Stress and VTA synapses: implications for addiction and depression. *European Journal of Neuroscience*, 39(7), 1179-1188.

Pomierny-Chamioło, L., Rup, K., Pomierny, B., Niedzielska, E., Kalivas, P. W., & Filip, M. (2014). Metabotropic glutamatergic receptors and their ligands in drug addiction. *Pharmacology & Therapeutics*, 142(3), 281-305.

Pontieri, F. E., Tanda, G., Orzi, F., & Di Chiara, G. (1996). Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature,* 382(6588), 255-257.

Popoli, M., Yan, Z., McEwen, B. S., & Sanacora, G. (2011). The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission.*Nature Reviews Neuroscience*, 13(1), 22-37.

Powell, K. (2006). Neurodevelopment: how does the teenage brain work?. *Nature*, 442(7105), 865-867.

Quadros, I. M., & Miczek, K. A. (2009). Two modes of intense cocaine bingeing: increased persistence after social defeat stress and increased rate of intake due to extended access conditions in rats. *Psychopharmacology*, 206(1), 109-120.

Quintero, G. C. (2013). Role of nucleus accumbens glutamatergic plasticity in drug addiction. *Neuropsychiatric Disease and Treatment*, 9, 1499-1512.

Ramirez, R. L., & Spear, L. P. (2010). Ontogeny of ethanol-induced motor impairment following acute ethanol: assessment via the negative geotaxis reflex in adolescent and adult rats. *Pharmacology Biochemistry and Behavior*, 95(2), 242-248.

Ramos, M., Goñi-Allo, B., & Aguirre, N. (2004). Studies on the role of dopamine D1 receptors in the development and expression of MDMA-induced behavioral sensitization in rats. *Psychopharmacology*, 177(1-2), 100-110.

Razzoli, M., Andreoli, M., Michielin, F., Quarta, D., & Sokal, D. M. (2011). Increased phasic activity of VTA dopamine neurons in mice 3 weeks after repeated social defeat. *Behavioural Brain Research*, 218(1), 253-257.

Reay, J. L., Hamilton, C., Kennedy, D. O., & Scholey, A. B. (2006). MDMA polydrug users show processspecific central executive impairments coupled with impaired social and emotional judgement processes. *Journal of Psychopharmacology*, 20(3), 385-388.

Reid, L. W., Elifson, K. W., & Sterk, C. E. (2007). Hug drug or thug drug? Ecstasy use and aggressive behavior. *Violence and Victims*, 22(1), 104-119.

Reneman, L., Booij, J., Majoie, C. B., van Den Brink, W., & Den Heeten, G. J. (2001). Investigating the potential neurotoxicity of Ecstasy (MDMA): an imaging approach. *Human Psychopharmacology: Clinical and Experimental*, 16(8), 579-588.

Renoir, T., Païzanis, E., El Yacoubi, M., Saurini, F., Hanoun, N., Melfort, M., ... & Lanfumey, L. (2008). Differential long-term effects of MDMA on the

serotoninergic system and hippocampal cell proliferation in 5-HTT knock-out vs. wild-type mice. *International Journal of Neuropsychopharmacology*, 11(8), 1149-1162.

Reveron, M. E., Maier, E. Y., & Duvauchelle, C. L. (2010). Behavioral, thermal and neurochemical effects of acute and chronic 3, 4-methylenedioxymethamphetamine ("Ecstasy") self-administration. *Behavioural Brain Research*, 207(2), 500-507.

Ricaurte, G. A., & McCann, U. D. (1992). Neurotoxic Amphetamine Analogues: Effects in Monkeys and Implications for Humansa. *Annals of the New York Academy of Sciences*, 648(1), 371-382.

Ricaurte, G. A., Forno, L. S., Wilson, M. A., DeLanney, L. E., Irwin, I., Molliver, M. E., & Langston, J. W. (1988). (±3, 4-Methylenedioxymethamphetamine Selectively Damages Central Serotonergic Neurons in Nonhuman Primates. *JAMA*, 260(1), 51-55.

Ricaurte, G. A., Yuan, J., Hatzidimitriou, G., Cord, B. J., & McCann, U. D. (2003). Response to O'Shea and Colado: the MDMA neurotoxicity profile might provide clues to mechanisms. *Trends in Pharmacological Sciences*, 24(6), 275.

Ricaurte, G., Bryan, G., Strauss, L., Seiden, L., & Schuster, C. (1985). Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science*, 229(4717), 986-988.

Rice, J. P., Suggs, L. E., Lusk, A. V., Parker, M. O., Candelaria-Cook, F. T., Akers, K. G., ... & Hamilton, D. A. (2012). Effects of exposure to moderate levels of ethanol during prenatal brain development on dendritic length, branching, and spine density in the nucleus accumbens and dorsal striatum of adult rats. *Alcohol*, 46(6), 577-584.

Ridley, N. J., Draper, B., & Withall, A. (2013). Alcohol-related dementia: an update of the evidence. *Alzheimer's Research & Therapy*, 5(1), 3.

Riekkinen, M., Stefanski, R., Kuitunen, J., & Riekkinen, P. (1996). Effects of combined block of α 1-adrenoceptors and NMDA receptors on spatial and passive avoidance behavior in rats. *European Journal of Pharmacology*, 300(1), 9-16.

Riga, D., Schmitz, L. J., van der Harst, J. E., van Mourik, Y., Hoogendijk, W. J., Smit, A. B., ... & Spijker, S. (2014). A sustained depressive state promotes a guanfacine reversible susceptibility to alcohol seeking in rats. *Neuropsychopharmacology*, 39(5), 1115-1124.

Ristuccia, R. C., & Spear, L. P. (2008). Autonomic responses to ethanol in adolescent and adult rats: a dose–response analysis. *Alcohol*, 42(8), 623-629.

Robbins, T. W., & Everitt, B. J. (1999). Drug addiction: bad habits add up. *Nature*, 398(6728), 567-570.

Robbins, T. W., & Everitt, B. J. (2002). Limbic-striatal memory systems and drug addiction. *Neurobiology of Learning and Memory*, 78(3), 625-636.

Roberts, C. A., Wetherell, M. A., Fisk, J. E., & Montgomery, C. (2014). Differences in prefrontal blood oxygenation during an acute multitasking stressor in ecstasy polydrug users. *Psychological Medicine*, in press.

Robinson, D. L., Howard, E. C., McConnell, S., Gonzales, R. A., & Wightman, R. M. (2009). Disparity Between Tonic and Phasic Ethanol-Induced Dopamine Increases in the Nucleus Accumbens of Rats. *Alcoholism: Clinical and Experimental Research*, 33(7), 1187-1196.

Rodd, Z. A., Bell, R. L., Melendez, R. I., Kuc, K. A., Lumeng, L., Li, T. K., ... & McBride, W. J. (2004). Comparison of Intracranial Self-Administration of Ethanol Within the Posterior Ventral Tegmental Area Between Alcohol-Preferring and Wistar Rats. *Alcoholism: Clinical and Experimental Research*, 28(8), 1212-1219.

Rodd, Z. A., Melendez, R. I., Bell, R. L., Kuc, K. A., Zhang, Y., Murphy, J. M., & McBride, W. J. (2004). Intracranial self-administration of ethanol within the ventral tegmental area of male Wistar rats: evidence for involvement of dopamine neurons. *The Journal of Neuroscience*, 24(5), 1050-1057.

Rodríguez-Arias, M., & Aguilar, M.A. (2012) Polydrug Use in Adolescence. In: Belin D, editor. Addictions – From Pathophysiology to Treatment. Chapter 8. InTechOpen. pp. 227-258.

Rodríguez-Arias, M., García-Pardo, M.P., Montagud-Romero, S., Miñarro, J., & Aguilar, M.A. (2013). The role of stress in psychostimulant addiction: treatment approaches based on animal models. In: Van Hout MC, editor. Drug use and abuse. Chapter 10. New York: Nova Science Publishers Inc. pp. 153–220.

Rodríguez-Arias, M., Maldonado, C., Vidal-Infer, A., Guerri, C., Aguilar, M. A., & Miñarro, J. (2011). Intermittent ethanol exposure increases long-lasting behavioral and neurochemical effects of MDMA in adolescent mice. *Psychopharmacology*, 218(2), 429-442.

Rodríguez-Arias, M., Manzanedo, C., Roger-Sánchez, C., Do Couto, B. R., Aguilar, M. A., & Miñarro, J. (2010). Effect of adolescent exposure to WIN 55212-2 on the acquisition and reinstatement of MDMA-induced conditioned place preference. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 34(1), 166-171.

Rodríguez-Arias, M., Minarro, J., Aguilar, M. A., Pinazo, J., & Simon, V. M. (1998). Effects of risperidone and SCH 23390 on isolation-induced aggression in male mice. *European Neuropsychopharmacology*, 8(2), 95-103.

Rodríguez-Arias, M., Montagud-Romero, S., Rubio-Araiz, A., Aguilar, M. A., Martín-García, E., Cabrera, R., … & Miñarro, J. Effects of Repeated Social Defeat to adolescent mice on cocaine-induced CPP and self-administration in adulthood: integrity of the blood-brain barrier. *Neuropsychopharmacology* (Submitted)

Rodríguez-Arias, M., Navarrete, F., Blanco-Gandia, M. C., Arenas, M. C., Bartoll-Andrés, A., Aguilar, M. A., ... & Manzanares, J. (2014). Social defeat in adolescent mice increases vulnerability to alcohol consumption. *Addiction Biology*. Sep 14.

Rodsiri, R., Spicer, C., Green, A. R., Marsden, C. A., & Fone, K. C. (2011). Acute concomitant effects of MDMA binge dosing on extracellular 5-HT, locomotion and body temperature and the long-term effect on novel object discrimination in rats. *Psychopharmacology*, 213(2-3), 365-376.

Roger-Sánchez, C., A Aguilar, M., Manzanedo, C., Miñarro, J., & Rodríguez-Arias, M. (2013)c. Neurochemical Substrates of MDMA Reward: Effects of the Inhibition of Serotonin Reuptake on the Acquisition and Reinstatement of MDMA-induced CPP. *Current Pharmaceutical Design*, 19(40), 7050-7064.

Roger-Sánchez, C., Aguilar, M. A., Rodríguez-Arias, M., Aragon, C. M., & Miñarro, J. (2012). Age-and sex-related differences in the acquisition and reinstatement of ethanol CPP in mice. *Neurotoxicology and Teratology*, 34(1), 108-115.

Roger-Sánchez, C., Rodríguez-Arias, M., Miñarro, J., & Aguilar, M. A. (2013)a. Effects of risperidone on the acquisition and reinstatement of the conditioned place preference induced by MDMA. *Brain Research Bulletin*, 98, 36-43.

Roger-Sánchez, C., Rodríguez-Arias, M., Miñarro, J., & Aguilar, M. A. (2013)b. Involvement of 5-hydroxytryptamine 5-HT_3 serotonergic receptors in the acquisition and reinstatement of the conditioned place preference induced by MDMA. *European Journal of Pharmacology*, 15;714(1-3), 132-141.

Romeo, R. D. (2010). Adolescence: a central event in shaping stress reactivity. *Developmental Psychobiology*, 52(3), 244-253.

Romero, A. M., Renau-Piqueras, J., Marin, M. P., Timoneda, J., Berciano, M. T., Lafarga, M., & Esteban-Pretel, G. (2013). Chronic alcohol alters dendritic spine development in neurons in primary culture. *Neurotoxicity Research*, 24(4), 532-548.

Rotter, A., Biermann, T., Amato, D., Schumann, G., Desrivieres, S., Kornhuber, J., & Müller, C. P. (2012). Glucocorticoid receptor antagonism blocks ethanol-induced place preference learning in mice and attenuates dopamine D2 receptor adaptation in the frontal cortex. *Brain Research Bulletin*, 88(5), 519-524.

Rouiné J., Kelly M. E. , Jennings-Murphy C., Duffy P., Gorman I., Gormley S., Kerskens C. M., & Harkin A. (2014). Investigation of the mechanisms mediating MDMA "Ecstasy"-induced increases in cerebro-cortical perfusion determined by btASL MRI. *Psychopharmacology*, in press.

Ruiz-Medina, J., Ledent, C., Carretón, O., & Valverde, O. (2011). The A2a adenosine receptor modulates the reinforcement efficacy and neurotoxicity of MDMA. *Journal of Psychopharmacology*, 25(4), 550-564.

Sakharkar, A. J., Tang, L., Zhang, H., Chen, Y., Grayson, D. R., & Pandey, S. C. (2014). Effects of acute ethanol exposure on anxiety measures and epigenetic

modifiers in the extended amygdala of adolescent rats. *International Journal of Neuropsychopharmacology*, 17(12), 2057-2067.

Sakharkar, A. J., Zhang, H., Tang, L., Shi, G., & Pandey, S. C. (2012). Histone Deacetylases (HDAC)-Induced Histone Modifications in the Amygdala: A Role in Rapid Tolerance to the Anxiolytic Effects of Ethanol. *Alcoholism: Clinical and Experimental Research*, 36(1), 61-71.

Samson, H. H., & Czachowski, C. L. (2003). Behavioral measures of alcohol self-administration and intake control: rodent models. *International Review of Neurobiology*, 107-145.

Sanday, L., Patti, C. L., Zanin, K. A., Fernandes-Santos, L., Oliveira, L. C., Kameda, S. R., ... & Frussa-Filho, R. (2013). Ethanol-Induced Memory Impairment in a Discriminative Avoidance Task is State-Dependent. *Alcoholism: Clinical and Experimental Research*, 37(S1), E30-E39.

Sarasa-Renedo, A., Sordo, L., Molist, G., Hoyos, J., Guitart, A. M., & Barrio, G. (2014). Health and social harm related alcohol. *Revista Española de Salud Pública*, 88(4), 469-491.

Sarnyai, Z., & Kovács, G. L. (2014). Oxytocin in learning and addiction: from early discoveries to the present. *Pharmacology Biochemistry and Behavior*, 119, 3-9.

Sarnyai, Z., Shaham, Y., & Heinrichs, S. C. (2001). The role of corticotropin-releasing factor in drug addiction. *Pharmacological Reviews*, 53(2), 209-244.

Schenk, S., Gittings, D., & Colussi-Mas, J. (2011). Dopaminergic mechanisms of reinstatement of MDMA-seeking behaviour in rats. *British journal of Pharmacology*, 162(8), 1770-1780.

Schenk, S., Hely, L., Gittings, D., Lake, B., & Daniela, E. (2008). Effects of priming injections of MDMA and cocaine on reinstatement of MDMA-and cocaine-seeking in rats. *Drug and Alcohol Dependence*, 96(3), 249-255.

Schenk, S., Hely, L., Lake, B., Daniela, E., Gittings, D., & Mash, D. C. (2007). MDMA self-administration in rats: acquisition, progressive ratio responding and

serotonin transporter binding. *European Journal of Neuroscience*, 26(11), 3229-3236.

Schifano, F., Corkery, J., Naidoo, V., Oyefeso, A., & Ghodse, H. (2010). Overview of amphetamine-type stimulant mortality data-UK, 1997-2007.*Neuropsychobiology*, 61(3), 122.

Schmidt, C. J. (1987). Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *Journal of Pharmacology and Experimental Therapeutics*, 240(1), 1-7.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology*, 13(2), 253-263.

Scholey, A. B., Owen, L., Gates, J., Rodgers, J., Buchanan, T., Ling, J., ... & Parrott, A. C. (2011). Hair MDMA samples are consistent with reported ecstasy use: findings from a study investigating effects of ecstasy on mood and memory. *Neuropsychobiology*, 63(1), 15-21.

Schramm-Sapyta, N. L., Walker, Q. D., Caster, J. M., Levin, E. D., & Kuhn, C. M. (2009). Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. *Psychopharmacology*, 206(1), 1-21.

Schuman, E. M., Meffert, M. K., Schulman, H., & Madison, D. V. (1994). An ADP-ribosyltransferase as a potential target for nitric oxide action in hippocampal long-term potentiation. *Proceedings of the National Academy of Sciences*, 91(25), 11958-11962.

Selvaraj, S., Hoshi, R., Bhagwagar, Z., Murthy, N. V., Hinz, R., Cowen, P., ... & Grasby, P. (2009). Brain serotonin transporter binding in former users of MDMA ('ecstasy'). *The British Journal of Psychiatry*, 194(4), 355-359.

Semple, D. M., Ebmeier, K. P., Glabus, M. F., O'Carroll, R. E., & Johnstone, E. C. (1999). Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *The British Journal of Psychiatry*, 175(1), 63-69.

Serrano, A., & Parsons, L. H. (2011). Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. *Pharmacology & Therapeutics*, 132(3), 215-241.

Sessa, B. (2007). Is there a case for MDMA-assisted psychotherapy in the UK?. *Journal of Psychopharmacology*, 21(2), 220-224.

Shankaran, M., & Gudelsky, G. A. (1998). Effect of 3, 4-methylenedioxymethamphetamine (MDMA) on hippocampal dopamine and serotonin. *Pharmacology Biochemistry and Behavior*, 61(4), 361-366.

Shariati, M. B. H., Sohrabi, M., Shahidi, S., Nikkhah, A., Mirzaei, F., Medizadeh, M., & Asl, S. S. (2014). Acute effects of ecstasy on memory are more extensive than chronic effects. *Basic and Clinical Neuroscience*, 5(3), 225.

Sherlock, K., Wolff, K., Hay, A. W., & Conner, M. (1999). Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. *Journal of Accident & Emergency Medicine*, 16(3), 194-197.

Shippenberg, T. S., Zapata, A., & Chefer, V. I. (2007). Dynorphin and the pathophysiology of drug addiction. *Pharmacology & Therapeutics*, 116(2), 306-321.

Shortall, S. E., Macerola, A. E., Swaby, R. T., Jayson, R., Korsah, C., Pillidge, K. E., ... & King, M. V. (2013). Behavioural and neurochemical comparison of chronic intermittent cathinone, mephedrone and MDMA administration to the rat. *European Neuropsychopharmacology*, 23(9), 1085-1095.

Shulgin, A. T. (1990). History of MDMA. In: *Peroutka S. J., editor. Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA.* Kluwer Academic Publishers. pp. 1-20.

Silva, M., Aguiar, D. C., Diniz, C. R., Guimaraes, F. S., & Joca, S. R. (2012). Neuronal NOS inhibitor and conventional antidepressant drugs attenuate stress-induced fos expression in overlapping brain regions. *Cellular and Molecular Neurobiology*, 32(3), 443-453.

Silvers, J. M., Tokunaga, S., Berry, R. B., White, A. M., & Matthews, D. B. (2003). Impairments in spatial learning and memory: ethanol, allopregnanolone, and the hippocampus. *Brain Research Reviews*, 43(3), 275-284.

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse?. *Psychopharmacology*, 158(4), 343-359.

Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences*, 1141(1), 105-130.

Sinha, R., Fox, H. C., Hong, K. I. A., Hansen, J., Tuit, K., & Kreek, M. J. (2011). Effects of adrenal sensitivity, stress-and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. *Archives of General Psychiatry*, 68(9), 942-952.

Sisk, C. L., & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature Neuroscience*, 7(10), 1040-1047.

Skelton, M. R., Williams, M. T., & Vorhees, C. V. (2006). Treatment with MDMA from P11–20 disrupts spatial learning and path integration learning in adolescent rats but only spatial learning in older rats. *Psychopharmacology*, 189(3), 307-318.

Skelton, M. R., Williams, M. T., & Vorhees, C. V. (2008). Developmental effects of 3, 4-methylenedioxymethamphetamine: a review. *Behavioural Pharmacology*, 19(2), 91.

Smith, K. L., John, C. S., Sypek, E. I., Öngür, D., Cohen, B. M., Barry, S. M., & Bechtholt, A. J. (2014). Exploring the Role of Central Astrocytic Glutamate Uptake in Ethanol Reward in Mice. *Alcoholism: Clinical and Experimental Research*, 38(5), 1307-1314.

Söderpalm, B., & Ericson, M. (2013). Neurocircuitry involved in the development of alcohol addiction: the dopamine system and its access points. *Current Topics in Behavioral Neurosciences,* 13, 127-161.

Solinas, M., Yasar, S., & Goldberg, S. R. (2007). Endocannabinoid system involvement in brain reward processes related to drug abuse. *Pharmacological Research*, 56(5), 393-405.

Song, M., Wang, X. Y., Zhao, M., Wang, X. Y., Zhai, H. F., & Lu, L. (2007). Role of Stress in Acquisition of Alcohol-Conditioned Place Preference in Adolescent and Adult Mice. *Alcoholism: Clinical and Experimental Research*, 31(12), 2001-2005.

Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine & Child Neurology*, 44(1), 4-16.

Spanagel, R. (2009). Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiological Reviews*, 89(2), 649-705.

Spanagel, R., Noori, H. R., & Heilig, M. (2014). Stress and alcohol interactions: animal studies and clinical significance. *Trends in Neurosciences*, *37*(4), 219-227.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews*, 24(4), 417-463.

Spear, L. P. (2011). Adolescent neurobehavioral characteristics, alcohol sensitivities, and intake: Setting the stage for alcohol use disorders?. *Child Development Perspectives*, 5(4), 231-238.

Spiga, S., Talani, G., Mulas, G., Licheri, V., Fois, G. R., Muggironi, G., ... & Diana, M. (2014). Hampered long-term depression and thin spine loss in the nucleus accumbens of ethanol-dependent rats. *Proceedings of the National Academy of Sciences*, 111(35), E3745-E3754.

Steru, L., Chermat, R., Thierry, B., & Simon, P. (1985). The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology*, 85(3), 367-370.

Stewart, R. B., Murphy, J. M., McBride, W. J., Lumeng, L., & Li, T. K. (1996). Place conditioning with alcohol in alcohol-preferring and-nonpreferring rats. *Pharmacology Biochemistry and Behavior*, 53(3), 487-491.

Stone, D. M., Stahl, D. C., Hanson, G. R., & Gibb, J. W. (1986). The effects of 3, 4-methylenedioxymethamphetamine (MDMA) and 3, 4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. *European Journal of Pharmacology*, 128(1), 41-48.

Stone, E. A., & Quartermain, D. (1997). Greater behavioral effects of stress in immature as compared to mature male mice. *Physiology & Behavior*, 63(1), 143-145.

Sturman, D. A., & Moghaddam, B. (2011). Reduced neuronal inhibition and coordination of adolescent prefrontal cortex during motivated behavior. *The Journal of Neuroscience*, 31(4), 1471-1478.

Sutherland G. T., Sheedy D, Kril J. J. (2014). Neuropathology of alcoholism. *Handbook* of *Clinical Neurology,* 125, 603-615.

Suto, N., Tanabe, L. M., Austin, J. D., Creekmore, E., & Vezina, P. (2003). Previous exposure to VTA amphetamine enhances cocaine self-administration under a progressive ratio schedule in an NMDA, AMPA/kainate, and metabotropic glutamate receptor-dependent manner. *Neuropsychopharmacology,* 28(4), 629-639.

Suy, K., Gijsenbergh, F., & Baute, L. (1999). Emergency medical assistance during a mass gathering. *European Journal of Emergency Medicine*, 6(3), 249-254.

Suzdak, P. D., Schwartz, R. D., Skolnick, P., & Paul, S. M. (1986). Ethanol stimulates gamma-aminobutyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. *Proceedings of the National Academy of Sciences*, 83(11), 4071-4075.

Szabo, Z., McCann, U. D., Wilson, A. A., Scheffel, U., Owonikoko, T., Mathews, W. B., ... & Ricaurte, G. A. (2002). Comparison of (+)-11C-McN5652 and 11C-DASB as serotonin transporter radioligands under various experimental conditions. *Journal of Nuclear Medicine*, 43(5), 678-692.

Szalontay A. S. Physiopathological and therapeutical correlations in alcohol dependence. (2014). *Medical-Surgical Journal*, 118(3), 692-698.

Taffe, M. A., Lay, C. C., Von Huben, S. N., Davis, S. A., Crean, R. D., & Katner, S. N. (2006). Hyperthermia induced by 3, 4-methylenedioxymethamphetamine in unrestrained rhesus monkeys. *Drug and Alcohol Dependence*, 82(3), 276-281.

Taffe, M. A., Weed, M. R., Davis, S., Huitrón-Resendiz, S., Schroeder, R., Parsons, L. H., ... & Gold, L. H. (2001). Functional consequences of repeated (±) 3, 4-methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. *Neuropsychopharmacology*, 24(3), 230-239.

Tanchuck-Nipper, M. A., Ford, M. M., Hertzberg, A., Beadles-Bohling, A., Cozzoli, D. K., & Finn, D. A. (2014). Sex differences in ethanol's anxiolytic effect and chronic ethanol withdrawal severity in mice with a null mutation of the 5α-reductase type 1 gene. *Behavior Genetics*, in press.

Taurah, L., Chandler, C., & Sanders, G. (2014). Depression, impulsiveness, sleep, and memory in past and present polydrug users of 3, 4-methylenedioxymethamphetamine (MDMA, ecstasy). *Psychopharmacology*, 231(4), 737-751.

Teixeira-Gomes, A., Costa, V. M., Feio-Azevedo, R., de Lourdes Bastos, M., Carvalho, F., & Capela, J. P. S. (2014). The neurotoxicity of amphetamines during the adolescent period. *International Journal of Developmental Neuroscience*, 41C, 44-62.

Thompson, M. R., Callaghan, P. D., Hunt, G. E., & McGregor, I. S. (2008). Reduced sensitivity to MDMA-induced facilitation of social behaviour in MDMA pre-exposed rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 32(4), 1013-1021.

Thompson, M. R., Hunt, G. E., & McGregor, I. S. (2009). Neural correlates of MDMA ("Ecstasy")-induced social interaction in rats. *Social Neuroscience*, 4(1), 60-72.

Thompson, M. R., Li, K. M., Clemens, K. J., Gurtman, C. G., Hunt, G. E., Cornish, J. L., & McGregor, I. S. (2004). Chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA ('Ecstasy') in rats. *Neuropsychopharmacology*, 29(4), 694-704.

Tomek, S. E., LaCrosse, A. L., Nemirovsky, N. E., & Olive, M. F. (2013). NMDA receptor modulators in the treatment of drug addiction. *Pharmaceuticals*, 6(2), 251-268.

Tornatzky, W., & Miczek, K. A. (1993). Long-term impairment of autonomic circadian rhythms after brief intermittent social stress. *Physiology & Behavior*, 53(5), 983-993.

Torres, E., Gutierrez-Lopez, M. D., Mayado, A., Rubio, A., O'Shea, E., & Colado, M. I. (2011). Changes in interleukin-1 signal modulators induced by 3, 4-methylenedioxymethamphetamine (MDMA): regulation by CB2 receptors and implications for neurotoxicity. *Neuroinflammation*, 8, 53.

Touriño, C., Ledent, C., Maldonado, R., & Valverde, O. (2008). CB 1 cannabinoid receptor modulates 3, 4-methylenedioxymethamphetamine acute responses and reinforcement. *Biological Psychiatry*, 63(11), 1030-1038.

Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K. K., ... & Dingledine, R. (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacological Reviews*, 62(3), 405-496.

Trigo, J. M., Cabrero-Castel, A., Berrendero, F., Maldonado, R., & Robledo, P. (2008). MDMA modifies active avoidance learning and recall in mice. *Psychopharmacology*, 197(3), 391-400.

Trigo, J. M., Panayi, F., Soria, G., Maldonado, R., & Robledo, P. (2006). A reliable model of intravenous MDMA self-administration in naive mice. *Psychopharmacology*, 184(2), 212-220.

Trigo, J. M., Renoir, T., Lanfumey, L., Hamon, M., Lesch, K. P., Robledo, P., & Maldonado, R. (2007). 3, 4-methylenedioxymethamphetamine self-administration is abolished in serotonin transporter knockout mice. *Biological Psychiatry*, 62(6), 669-679.

Turnbull, A. V., & Rivier, C. (1997). Corticotropin-releasing factor (CRF) and endocrine responses to stress: CRF receptors, binding protein, and related peptides. *Experimental Biology and Medicine*, 215(1), 1-10.

Turner, J. J., Parrott, A. C., Goodwin, J., Moore, D. G., Fulton, S., Min, M. O., & Singer, L. T. (2014). Psychiatric profiles of mothers who take Ecstasy/MDMA during pregnancy: Reduced depression 1 year after giving birth and quitting Ecstasy. *Journal of Psychopharmacology*, 28(1), 55-61.

Tzschentke, T. M. (2007). Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. *Addiction Biology,* 12(3-4):227-462.

Uosukainen, H., Tacke, U., & Winstock, A. R. (2015). Self-reported prevalence of dependence of MDMA compared to cocaine, mephedrone and ketamine among a sample of recreational poly-drug users. *International Journal of Drug Policy*, 26(1), 78-83.

Vallés, S. L., Blanco, A. M., Pascual, M., & Guerri, C. (2004). Chronic ethanol treatment enhances inflammatory mediators and cell death in the brain and in astrocytes. *Brain Pathology*, 14(4), 365-371.

Valverde, O., & Rodriguez-Arias, M. (2013). Modulation of 3, 4-Methylenedioxymethamphetamine Effects by Endocannabinoid System. *Current Pharmaceutical Design*, 19(40), 7081-7091.

Van den Oever, M. C., Spijker, S., & Smit, A. B. (2012). The synaptic pathology of drug addiction. *Advances in Experimental Medicine and Biology*, 970, 469-491.

van Erp, A. M., & Miczek, K. A. (2001). Persistent suppression of ethanol self-administration by brief social stress in rats and increased startle response as index of withdrawal. *Physiology & Behavior*, 73(3), 301-311.

van Huijstee A. N. & Mansvelder H. D. (2015). Glutamatergic synaptic plasticity in the mesocorticolimbic system in addiction. *Frontiers in Human Neuroscience,* 8, 466.

Van Skike, C. E., Botta, P., Chin, V. S., Tokunaga, S., McDaniel, J. M., Venard, J., ... & Matthews, D. B. (2010). Behavioral effects of ethanol in cerebellum are age dependent: potential system and molecular mechanisms. *Alcoholism: Clinical and Experimental Research*, 34(12), 2070-2080.

Varela M. J., Brea J., Loza M. I., Maldonado R., & Robledo P. Sensitization to MDMA locomotor effects and changes in the functionality of 5-HT(2A) and D_2 receptors in mice. (2011). *Behavioural Pharmacology,* 22(4), 362-9.

Vázquez, D. M. (1998). Stress and the developing limbic–hypothalamic–pituitary–adrenal axis. *Psychoneuroendocrinology*, 23(7), 663-700.

Verbaten, M. N. (2003). Specific memory deficits in ecstasy users? The results of a meta-analysis. *Human Psychopharmacology: Clinical and Experimental*,18(4), 281-290.

Verendeev, A., & Riley, A. L. (2013). The role of the aversive effects of drugs in self-administration: assessing the balance of reward and aversion in drug-taking behavior. *Behavioural Pharmacology*, 24(5 and 6), 363-374.

Verkes, R. J., Gijsman, H. J., Pieters, M. S., Schoemaker, R. C., de Visser, S., Kuijpers, M., ... & Cohen, A. F. (2001). Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology,* 153(2), 196-202.

Vidal-Infer, A., Aguilar, M. A., Miñarro, J., & Rodríguez-Arias, M. (2012)b. Effect of intermittent exposure to ethanol and MDMA during adolescence on learning and memory in adult mice. *Behavioral* and *Brain Functions*, 8(1), 32-32.

Vidal-Infer, A., Roger-Sánchez, C., Daza-Losada, M., Aguilar, M. A., Miñarro, J., & Rodríguez-Arias, M. (2012)a. Role of the dopaminergic system in the acquisition, expression and reinstatement of MDMA-induced conditioned place preference in adolescent mice. *PLoS One*, 7(8), e43107.

Vinod, K. Y., & Hungund, B. L. (2005). Endocannabinoid lipids and mediated system: Implications for alcoholism and neuropsychiatric disorders. *Life Sciences*, 77(14), 1569-1583.

Viñals, X., Maldonado, R., & Robledo, P. (2013). Effects of repeated treatment with MDMA on working memory and behavioural flexibility in mice. *Addiction Biology*, 18(2), 263-273.

Von Huben, S. N., Lay, C. C., Crean, R. D., Davis, S. A., Katner, S. N., & Taffe, M. A. (2007). Impact of ambient temperature on hyperthermia induced by (±) 3, 4-

methylenedioxymethamphetamine in rhesus macaques. *Neuropsychopharmacology*, 32(3), 673-681.

Wagner, D., Adolph, S.,, Koester, P.,, Becker, B.,, Gouzoulis-Mayfrank ,E.,, & Daumann, J. (2014). Interactions between specific parameters of MDMA use and cognitive and psychopathological measures. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 58:32-37.

Walker B. M., & Koob GF. Regarding "Dynorphin is a downstream effector of striatal BDNF regulation of ethanol intake". (2008)b. *FASEB,* 22(7), 2113; author reply 2113-4.

Walker, B. M., & Koob, G. F. (2008)a. Pharmacological evidence for a motivational role of κ-opioid systems in ethanol dependence. *Neuropsychopharmacology*, 33(3), 643-652.

Walker, B. M., Valdez, G. R., McLaughlin, J. P., & Bakalkin, G. (2012). Targeting dynorphin/kappa opioid receptor systems to treat alcohol abuse and dependence. *Alcohol*, 46(4), 359-370.

Walker, C. D., Trottier, G., Rochford, J., & Lavallée, D. (1995). Dissociation between behavioral and hormonal responses to the forced swim stress in lactating rats. *Journal of Neuroendocrinology*, 7(8), 615-622.

Wallace, T. L., Gudelsky, G. A., & Vorhees, C. V. (2001). Alterations in diurnal and nocturnal locomotor activity in rats treated with a monoamine-depleting regimen of methamphetamine or 3, 4-methylenedioxymethamphetamine. *Psychopharmacology*, 153(3), 321-326.

Wee, S., & Koob, G. F. (2010). The role of the dynorphin–κ opioid system in the reinforcing effects of drugs of abuse. *Psychopharmacology*, *210*(2), 121-135.

Wetherell, M. A., & Montgomery, C. (2014). Basal functioning of the hypothalamic-pituitary-adrenal (HPA) axis and psychological distress in recreational ecstasy polydrug users. *Psychopharmacology*, 231(7), 1365-1375.

Wetherell, M. A., Atherton, K., Grainger, J., Brosnan, R., & Scholey, A. B. (2012). The effects of multitasking on psychological stress reactivity in recreational

users of cannabis and MDMA. *Human Psychopharmacology: Clinical and Experimental*, 27(2), 167-176.

White, A. M., Bae, J. G., Truesdale, M. C., Ahmad, S., Wilson, W. A., & Swartzwelder, H. S. (2002)a. Chronic-Intermittent Ethanol Exposure During Adolescence Prevents Normal Developmental Changes in Sensitivity to Ethanol-Induced Motor Impairments. *Alcoholism: Clinical and Experimental Research*, 26(7), 960-968.

White, A. M., Truesdale, M. C., Bae, J. G., Ahmad, S., Wilson, W. A., Best, P. J., & Swartzwelder, H. S. (2002)b. Differential effects of ethanol on motor coordination in adolescent and adult rats. *Pharmacology Biochemistry and Behavior*, 73(3), 673-677.

White, S. R., Duffy, P., & Kalivas, P. W. (1994). Methylenedioxymethamphetamine depresses glutamate-evoked neuronal firing and increases extracellular levels of dopamine and serotonin in the nucleus accumbens in vivo. *Neuroscience*, 62(1), 41-50.

White, S. R., Obradovic, T., Imel, K. M., & Wheaton, M. J. (1996). The effects of methylenedioxymethamphetamine (MDMA,"Ecstasy") on monoaminergic neurotransmission in the central nervous system. *Progress in Neurobiology*, 49(5), 455-479.

Wirkner, K., Poelchen, W., Köles, L., Mühlberg, K., Scheibler, P., Allgaier, C., & Illes, P. (1999). Ethanol-induced inhibition of NMDA receptor channels. *Neurochemistry International*, 35(2), 153-162.

Wise, R. A. (1998). Drug-activation of brain reward pathways. *Drug and Alcohol Dependence*, 51(1), 13-22.

Wise, R. A. (2008). Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotoxicity Research*, 14(2-3), 169-183.

Wise, R. A., & Morales, M. (2010). A ventral tegmental CRF–glutamate–dopamine interaction in addiction. *Brain Research*, 1314, 38-43.

Wolfer, D. P., & Lipp, H. P. (1995). Evidence for physiological growth of hippocampal mossy fiber collaterals in the guinea pig during puberty and adulthood. *Hippocampus*, 5(4), 329-340.

Yamamoto, B. K., & Spanos, L. J. (1988). The acute effects of methylenedioxymethamphetamine on dopamine release in the awake-behaving rat. *European journal of Pharmacology*, 148(2), 195-203.

Yap, J. J., Chartoff, E. H., Holly, E. N., Potter, D. N., Carlezon Jr, W. A., & Miczek, K. A. (2014). Social defeat stress-induced sensitization and escalated cocaine self-administration: the role of ERK signaling in the rat ventral tegmental area. *Psychopharmacology*, in press.

Yap, J. J., Covington III, H. E., Gale, M. C., Datta, R., & Miczek, K. A. (2005). Behavioral sensitization due to social defeat stress in mice: antagonism at mGluR5 and NMDA receptors. *Psychopharmacology*, 179(1), 230-239.

Yap, J. J., Takase, L. F., Kochman, L. J., Fornal, C. A., Miczek, K. A., & Jacobs, B. L. (2006). Repeated brief social defeat episodes in mice: effects on cell proliferation in the dentate gyrus. *Behavioural Brain Research*, 172(2), 344-350.

Yoshimoto, K., McBride, W. J., Lumeng, L., & Li, T. K. (1992). Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. *Alcohol*, 9(1), 17-22.

Yubero-Lahoz, S., Kuypers, K. P. C., Ramaekers, J. G., Langohr, K., Farré, M., & de la Torre, R. (2014). Changes in serotonin transporter (5-HTT) gene expression in peripheral blood cells after MDMA intake. *Psychopharmacology,* in press.

Zakzanis, K. K., Campbell, Z., & Jovanovski, D. (2007). The neuropsychology of ecstasy (MDMA) use: a quantitative review. *Human Psychopharmacology: Clinical and Experimental,* 22(7), 427-435.

Zhang, J., Fan, Y., Li, Y., Zhu, H., Wang, L., & Zhu, M. Y. (2012). Chronic social defeat up-regulates expression of the serotonin transporter in rat dorsal raphe nucleus and projection regions in a glucocorticoid-dependent manner. *Journal of Neurochemistry*, 123(6), 1054-1068.

Zhou, F. C., Anthony, B., Dunn, K. W., Lindquist, W. B., Xu, Z. C., & Deng, P. (2007). Chronic alcohol drinking alters neuronal dendritic spines in the brain reward center nucleus accumbens. *Brain Research*, 1134 (1), 148-161.

Zhou, Y., Bendor, J., Hofmann, L., Randesi, M., Ho, A., & Kreek, M. J. (2006). Mu opioid receptor and orexin/hypocretin mRNA levels in the lateral hypothalamus and striatum are enhanced by morphine withdrawal. *Journal of Endocrinology*, 191(1), 137-145.

Zhou, Y., Colombo, G., Niikura, K., Carai, M. A., Femenía, T., García-Gutiérrez, M. S., ... & Kreek, M. J. (2013). Voluntary Alcohol Drinking Enhances Proopiomelanocortin Gene Expression in Nucleus Accumbens Shell and Hypothalamus of Sardinian Alcohol-Preferring Rats. *Alcoholism: Clinical and Experimental Research*, 37(s1), E131-E140.

Zorumski, C. F., Mennerick, S., & Izumi, Y. (2014). Acute and chronic effects of ethanol on learning-related synaptic plasticity. *Alcohol*, 48(1), 1-17.