THE ROLE OF DOPAMINE D_2 RECEPTOR MECHANISMS IN THE DEVELOPMENT OF MDMA SENSITISATION.

by

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Abstract

Rationale. ±3, 4-methelynedioxymethamphetamine (MDMA) is the primary psychoactive ingredient of the increasingly popular recreational street drug, ecstasy. As with other drugs of abuse, repeated intermitted exposure to MDMA can lead to an increase in the subsequent behavioural effects of the drug. This phenomenon, termed behavioural sensitisation, has been attributed to sensitisation of central DAergic mechanisms considered to underlie several aspects of addiction.

Objectives. The purpose of the present research was to investigate the role of DA D_2 receptor mechanisms in the development of MDMA sensitisation and the acquisition of MDMA self-administration in rats.

Methods. Rats received daily i.p. injections of the selective D_2 antagonist, eticlopride (0.0, 0.05, 0.3 mg/kg), prior to injections of MDMA (0.0, 10.0 mg/kg) for five days. Two days following the final pre-treatment session, the locomotor activating effects of MDMA (5 mg/kg, i.p.) were determined. Another group of rats were surgically implanted with i.v. jugular catheters before undergoing the same pre-treatment regimen. Two days following the final pre-treatment session, these rats were subsequently tested for acquisition of MDMA self-administration. The locomotor activating effects of MDMA (5 mg/kg i.p.) were determined two days following the last self-administration session.

Results. Pre-treatment with MDMA enhanced the locomotor activating effects of MDMA and facilitated the acquisition of MDMA self-administration, as evidenced by an increased likelihood to meet an acquisition criterion. Co-administration of eticlopride during pre-treatment completely blocked the development of sensitisation to MDMA-produced hyperactivity but failed to significantly attenuate the facilitation of MDMA self-administration. Interestingly, pre-treatment with eticlopride alone also facilitated the acquisition of self-administration. MDMA self-administration failed to alter MDMA-produced locomotor hyperactivity.

Conclusions. These findings suggest that repeated activation of DA D_2 receptors is required for the development of sensitisation to MDMA-produced hyperactivity but not for the development of sensitisation to MDMA-produced reinforcement. D_2 receptor mechanisms evidently play some role, however, because repeated exposure to eticlopride also facilitated MDMA self-administration. It is suggested that both sensitised DAergic mechanisms and desensitised 5-HTergic mechanisms contribute to the acquisition of MDMA self-administration.

Introduction

History of MDMA

In 1912, the German pharmaceutical company, Merck, was interested in finding an alternate means of producing the antihemorrhagic drug, hydrastinine. Merck chemist, Atnon Köllisch, first synthesised ±3, 4-methelynedioxymethamphetamine (MDMA) as one of the intermediate compounds required to produce a methylated analogue of hydrastinine, methylhydrastinine (Bernschneider-Reif, Öxler, & Freudenmann, 2006; Freudenmann, Oxler, & Bernschneider-Reif, 2006). On December 24th, 1912, Merck applied for the procedural patents of methylhydrastinine and the precursor compounds involved in its synthesis, including MDMA (Merck, 1912a, 1912b) Over the next 5 decades, Merck records indicate MDMA was investigated sporadically, however, details of this research is scant (Bernschneider-Reif et al., 2006; Freudenmann et al., 2006).

The first detailed research on MDMA was a toxicology study commissioned by the United States army in 1953 (Hardman, Haavik, & Seevers, 1973). Two decades later, the first report investigating the effects of MDMA in humans was published by Shulgin & Nichols (1978). They described the drug as inducing "an easily controlled altered state of consciousness with emotional and sensual overtones" (Shulgin & Nichols, 1978, p. 77). As promoted by Shulgin, MDMA began to be used as an adjunct to psychotherapy throughout the US (Beck, 1990; Shulgin, 2012). However, a dramatic increase in recreational use during the early 1980's prompted the Drug Enforcement Administration to propose for the scheduling of MDMA which was later granted in 1985 (Beck, 1990; Lawn, 1985). In 1987, New Zealand followed suit and scheduled MDMA as a Class B1 substance (Ministry of Health, 1975). In the United Kingdom, MDMA was already classified as a Class A drug since 1977 (Parliament of the United Kingdom, 1971).

Despite its criminalisation in most countries, recreational use of MDMA continued to rise. MDMA was primarily being used by young people at festivals, parties, and dance clubs (Johnston, 2010; McDowell & Kleber, 1994). Throughout the 1980's and 1990's, the increasing popularity of the rave subculture led to widespread use of MDMA, with it being one of the most commonly used illicit drugs at dance parties (Brown, Jarvie, & Simpson, 1995; Engels & ter Bogt, 2004; Lenton, Boys, & Norcross, 1997; Parks & Kennedy, 2004; Weir, 2000; Wilkins, Bhatta, Pledger, & Casswell, 2003). Today, use of MDMA has spread to mainstream populations, as consumption patterns and contexts of use have become more variable (Degenhardt, Barker, & Topp, 2004; Hansen, Maycock, & Lower,

2001; von Sydow, Lieb, Pfister, Höfler, & Wittchen, 2002; Wilkins, Prasad, Wong, & Rychert, 2014).

It should be noted that MDMA is typically consumed in pills or tablets often containing a number of other compounds (Parrott, 2004). For example, recent testing of pills seized by the New Zealand police revealed traces of benzylpiperazine (BZP), trifluoromethylphenylpiperazine (TFMPP), methylmethcathinone (mephedrone), methylethcathinone (4-MEC), dimethylamylamine (DMAA), methylenedioxymethcathinone (methylone), and caffeine (as cited in Wilkins, Jawalkar, Moewaka Barnes, Parker, & Asiasiga, 2014). Thus when outside of a controlled laboratory setting, MDMA will be referred to by the street name of these pills: ecstasy (also known as E, eccy, XTC, Molly, Adam, disco biscuits, among a number of other names).

Prevalence of ecstasy

It is estimated that there are ~19 million current ecstasy users worldwide (United Nations Office on Drugs and Crime [UNODC], 2015). For comparison, there are approximately ~17 million cocaine users and ~182 million cannabis users (UNODC, 2015). In New Zealand and Australia, the annual prevalence of ecstasy use is particularly high, being among the highest in the world at 2.6% and 2.49%, respectively (Australian Institute of Health and Welfare, 2013; Ministry of Health, 2010; UNODC, 2015). For New Zealand, this is a 0.7% increase since 2003, where ecstasy continues to be the second most commonly used illicit drug after marijuana (Ministry of Health, 2003).

European countries, particularly the Netherlands and Belgium, are the largest producers of ecstasy (UNODC, 2015). This is reflected by the average price of an ecstasy tablet in Europe ranging from as low as 3.10€ in Poland to 12.54€ in the UK (Winstock, 2015). In New Zealand, the average price of an ecstasy tablet is the highest in the world at 25.15 € (Winstock, 2015). This price has been steadily declining, however (Wilkins, Prasad, et al., 2014), which might be related to the increased production of ecstasy tablets in south-east Asia (UNODC, 2015).

Effects of MDMA in humans

Ecstasy has been rated as the most pleasurable recreational drug (Winstock, 2015). The most commonly reported subjective effect of MDMA is an increased sense of ‘closeness’ with others (Peroutka, Newman, & Harris, 1988). Other subjective effects include increased sensory awareness, euphoria, enhanced insight, increased extraversion, elevated self-confidence, and modest sensory hallucinations (Downing, 1986; Liechti,

Gamma, & Vollenweider, 2001; Peroutka et al., 1988; Tancer & Johanson, 2003; Vollenweider, Gamma, Liechti, & Huber, 1998). The amphetamine-like physiological effects of MDMA include tachycardia, increased blood pressure, increased muscle tension, bruxism (teeth grinding), and dry mouth (Downing, 1986; Liechti et al., 2001; Peroutka et al., 1988; Tancer & Johanson, 2003; Vollenweider et al., 1998). Nausea and vomiting are occasionally reported side effects (Downing, 1986). MDMA also causes a significant increase in body temperature (Freedman, Johanson, & Tancer, 2005; Tancer & Johanson, 2003; Torre et al., 2006). Negative side effects are common on the day following MDMA use. These include muscle aches, fatigue, paranoia, restlessness, supressed appetite, delirium, depression, anxiety, and difficulty concentrating (Parrott & Lasky, 1998; Peroutka et al., 1988; Vollenweider et al., 1998). Indeed many ecstasy users take other drugs to relieve such effects (Boys, Marsden, & Strang, 2001; Topp, Hando, Dillon, Roche, & Solowij, 1999; Winstock, Griffiths, & Stewart, 2001).

Drug abuse/dependence

Harmful drug use poses a significant threat to the health and wellbeing of society. Tobacco, alcohol, and illicit drug use was estimated to account for 10.29% of years of life lost due to disability or premature death in 2010, making it a top contributor to the global burden of disease (Degenhardt et al., 2013; Lim et al., 2012). The economic ramifications of this are severe. For example, the crime, healthcare, road crashes, and loss of productivity associated with harmful use of alcohol and other drugs (excluding tobacco) cost New Zealand approximately $6.5 billion in the year 2006, which is equivalent to the Global Domestic Product (GDP) of New Zealand's agricultural ($6.7 billion) and finance industries ($7 billion; Slack, Nana, Webster, Stokes, & Wu, 2009).

The previous Diagnostic and Statistical manual of Mental disorders (DSM-IV-TR) describes drug abuse as a maladaptive pattern of substance use leading to impairments in meeting work, school, or home obligations, with recurring legal, social, or interpersonal problems (American Psychiatric Association [APA], 2000). Drug dependence is more severe, being characterised by a much larger intake of the substance over longer periods of time than was intended, unsuccessful efforts to control use, tolerance and/or withdrawal, and continued use despite knowledge of recurring psychological, social, and physical problems caused by the drug (APA, 2000).

The most recent DSM-5 combines drug abuse and dependence into a single disorder, substance use disorder, which is manifested by meeting at least 2 of the criteria

displayed in Table 1. Substance use disorder is sub classified by substance type and is measured along a continuum from mild (2 – 3 criteria) to severe (6+ criteria; APA, 2013).

Table 1.
DSM-5 substance use disorder criteria

1.	Taking the substance in larger amounts or for longer than you meant to.
2.	Wanting to cut down or stop using the substance but not managing to.
3.	Spending a lot of time getting, using, or recovering from use of the substance.
4.	Cravings and urges to use the substance.
5.	Not managing to do what you should at work, home, or school because of substance use.
6.	Continuing to use, even when it causes problems in relationships.
7.	Giving up important social, occupational, or recreational activities because of substance use.
8.	Using substances again and again, even when it puts you in danger.
9.	Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance.
10.	Needing more of the substance to get the effect you want (tolerance).
11.	Development of withdrawal symptoms, which can be relieved by taking more of the substance.

Source: American Psychiatric Association (2013)**.**

Ecstasy abuse/dependence

Early findings indicated that ecstasy use was generally self-limited, being used once a week in heavier users on average (Beck & Rosenbaum, 1994; Hammersley, 1999; Solowij, Hall, & Lee, 1992). Tolerance to the positive effects of the drug and an increase of the negative after effects were the main reasons for cessation of use (Solowij et al., 1992). These findings seemed to confirm the prevailing view at the time that ecstasy lacked the compulsive usage patterns typical of a drug of abuse/dependence (Downing, 1986; Nichols & Glennon, 1984).

However, more recent studies revealed a change in the self-limiting, occasional nature of ecstasy use. The number of ecstasy pills taken per session had escalated and use had become more frequent (Parrott, 2001; Pope Jr, Ionescu-Pioggia, & Pope, 2001). Ecstasy was being used at home or at friends' houses, not just at dance parties (Degenhardt et al., 2004; Hansen et al., 2001; Strote, Lee, & Wechsler, 2002; Topp, Hall, & Hando, 1997; Topp et al., 1999). Additionally, an increasing number of users reported injecting ecstasy (Topp et al., 1997, 1999). Tolerance to the positive subjective effects of ecstasy was being overcome by repeatedly self-administering the drug at increasing doses. For example, from a sample of 185 current ecstasy users, 83% of users reported significant

tolerance to the effects of the drug with 56% reporting that they had doubled the amount of ecstasy they take in a sitting in order to achieve similar effects compared to when they first started (Topp et al., 1997). While the positive effects of ecstasy decrease with repeated use, the amphetamine-like physiological effects can increase (Jansen, 1997; Peroutka, 1990), which has led to some users developing a severe amphetamine-like dependence (Jansen, 1999).

Several studies have documented an abuse/dependence syndrome among ecstasy users, based on DSM-IV criteria. Topp, Hall, and Hando (1997) found that 48% of their Australian sample of 185 current ecstasy users met DSM-IV criteria for drug dependence. They compared ecstasy use to binge drinking alcohol, as the majority of users did not use ecstasy on most days but still presented significant levels of ecstasy-related harm (Topp et al., 1997). In the US, 43% of ecstasy users met DSM-IV criteria for dependence and 34% meet the criteria for abuse (Cottler, Womack, Compton, & Ben-Abdallah, 2001). In a community survey of 3021 adolescents in Germany, 4% of males and 2.3% of females reported using ecstasy at least once; of these individuals, 20% met the DSM-IV criteria for abuse/dependence (P. Schuster, Lieb, Lamertz, & Wittchen, 1998). Yen and Hsu (2007) interviewed a sample of 200 adolescent Taiwanese ecstasy users and found that 22% meet adopted DSM-IV criteria for dependence. Finally, in a cross-national study, 15% and 59% of ecstasy users met DSM-IV criteria for abuse and dependence, respectively (Cottler, Leung, & Abdallah, 2009). The most prevalent dependence criteria were ‘continued use despite knowledge of physical/psychological problems’ and ‘withdrawal’ whereas the most prevalent abuse criteria were ‘physically hazardous use’ followed by ‘use despite knowledge of social problems’ (Cottler et al., 2009).

Some ecstasy users have reported symptoms that are used to define a substance use disorder in the more recent DSM-V. For example, some users reported (1) taking ecstasy in larger amounts or for longer than they meant to (Cottler et al., 2001); (2) wanting to cut down or stop using ecstasy but not managing to (Topp et al., 1997); (3) cravings and urges to use ecstasy (Hopper et al., 2006); (4) continuing to use, even when they knew they had a physical or psychological problem that could have been caused or made worse by ecstasy (Cottler et al., 2009; Yen & Hsu, 2007); (5) tolerance to the positive effects (Parrott, 2005; Peroutka et al., 1988); and (6) development of withdrawal symptoms (Cottler et al., 2001; McKetin et al., 2014).

It should be noted that polydrug use is particularly prevalent among ecstasy users, which complicates the interpretation of clinical data (Topp et al., 1999). For example, current ecstasy users aged 14 – 19 years had used cannabis (88.3%), amphetamine (70.1%), LSD (27.1%), or cocaine (22.4%) within the past year (Degenhardt et al., 2004). Other drugs are often taken concurrently with ecstasy, usually in attempt to enhance the positive effects of the drug or to reduce the comedown effects (Boys et al., 2001; Topp et al., 1999; Winstock et al., 2001).

Ecstasy abuse has been attributed to the onset of several psychopathologies including paranoid psychosis, mixed affective psychosis, hallucinations, panic attacks, depression, and anxiety (Cassidy & Ballard, 1994; McGuire, Cope, & Fahy, 1994; Parrott, Sisk, & Turner, 2000; Series, Boeles, Dorkins, & Peveler, 1994; Topp et al., 1999; Williamson, 1997). Even when controlling for polydrug use, Yen and Hsu (2007) found that ecstasy use increased the risk for developing severe psychopathology. Ecstasy use has also been associated with cognitive deficits in memory and decision making (Halpern et al., 2004; Parrott, Lees, Garnham, Jones, & Wesnes, 1998; Roiser, Rogers, Cook, & Sahakian, 2006).

Ecstasy/MDMA-induced hyperthermia, renal failure, hepatic toxicity, rhabdomyolysis, cardiac arrhythmia, and disseminated intravascular coagulation have contributed to a number of deaths (Chadwick, Curry, Linsley, Freemont, & Doran, 1991; Dykhuizen, Brunt, Atkinson, Simpson, & Smith, 1995; Fineschi & Masti, 1996; Freedman et al., 2005; García-Repetto et al., 2003; Khakoo, Coles, Armstrong, & Barry, 1995; Schifano et al., 2003; Screaton et al., 1992). Alarmingly, emergency medical treatment of ecstasy users across the globe has increased from 0.3% of users in 2013 to 0.9% of users in 2015 (UNODC, 2015). For comparison, 0.6% of cocaine users, 1.0% of marijuana users, and 1.2% of alcohol users required emergency medical treatment in 2015 (United Nations Office on Drugs and Crime [UNODC], 2015). With ecstasy/MDMA use being associated with reports of significant psychological morbidity and relatively high rates of dependence, coupled with the increasing number of users seeking emergency medical treatment, there is a need for a better scientific understanding of the drug and its effects.

Self-administration

Drug abuse research using human participants is limited by ethical considerations and the inability to control for several confounding variables such as polydrug use, drug purity, personal history, etc. (Carter & Griffiths, 2009; Schenk, 2009). Although drug

abuse is a human problem, the development of animal paradigms such as self-administration (Shaham, Shalev, Lu, De Wit, & Stewart, 2003), conditioned place preference (Tzschentke, 2007), and drug discrimination (Overton, 1987) allows for the control of several variables that limit human research. Animal models have provided valuable insight into the neurochemical and behavioural mechanisms underlying drug taking.

Since the development of the indwelling intravenous (i.v.) catheter (Weeks, 1962), reliable i.v. self-administration has been demonstrated in non-human primates (Deneau, Yanagita, & Seevers, 1969; Gerber & Stretch, 1975; Goldberg, Woods, & Schuster, 1971; Lamb & Griffiths, 1990; T. Thompson & Schuster, 1964), dogs (Risner & Jones, 1975), cats (Balster, Kilbey, & Ellinwood, 1976), rats (Collins, Weeks, Cooper, Good, & Russell, 1983; Weeks & Collins, 1964), and mice (Criswell, 1983). Self-administration has proved to be an excellent method for evaluating the abuse liability of drugs. Drugs that are abused by humans are readily self-administered by laboratory animals, whereas drugs that are not abused by humans generally do not maintain self-administration in laboratory animals (Deneau et al., 1969; O'Connor, Chapman, Butler, & Mead, 2011; C. R. Schuster & Thompson, 1969). Indeed, the pre-clinical screening of potentially new pharmaceutical drugs involves evaluating their abuse liability using the self-administration paradigm (Ator & Griffiths, 2003; Food and Drug Administration, 2010)

The standard self-administration paradigm involves a simple choice procedure. The depression of one (active) lever results in an infusion of the drug while the depression of another (inactive) lever has no programmed consequence. Significant preference for the active lever indicates that the drug is reinforcing, as it is maintaining the operant response of lever pressing (e.g. Corrigall & Coen, 1989; Schenk, Colussi-Mas, Do, & Bird, 2012; Williamson, 1997). Reversal of the levers results in the corresponding reversal of lever pressing (Goeders & Smith, 1983; Pickens & Harris, 1968). Replacement of the drug with saline results in the extinction of lever pressing, which can subsequently be reinstated by the reintroduction of the drug (e.g. Gerber & Stretch, 1975; Grove & Schuster, 1974; Pickens & Harris, 1968).

The dose effect curve for self-administration typically takes the form of an inverted U. Low doses of drug often fail to reinforce responding, but above a threshold dose, the drug will reinforce high levels of responding. Laboratory animals will typically dose-dependently alter their behavioural response in order to maintain a similar average daily

intake. That is, a lower infusion dose will result in more responses whereas a higher infusion dose will result in fewer responses (Goldberg, Hoffmeister, Schlichting, & Wuttke, 1971; Pickens & Harris, 1968; Weeks & Collins, 1964). Likewise, an increase in the fixed ratio (FR) will result in the proportional increase in the required behavioural response (Goldberg, Hoffmeister, et al., 1971; Pickens & Harris, 1968; Schenk et al., 2012).

MDMA self-administration

Early studies involved substituting cocaine for MDMA in self-administration trained non-human primates. In rhesus monkeys, an inverted U shaped function for MDMA responding was produced and three of the four animals responded at rates above saline levels (Beardsley, Balster, & Harris, 1986). Two of these subjects responded at rates similar to cocaine while one subject did not self-administer MDMA at any of the doses tested (Beardsley et al., 1986). Subsequent studies showed that although MDMA maintained responding at levels higher than saline, rates of responding were generally less than cocaine and often highly variable (Fantegrossi et al., 2004; Fantegrossi, Ullrich, Rice, Woods, & Winger, 2002; Lamb & Griffiths, 1987; Lile, Ross, & Nader, 2005).

Initial studies using naïve rats reported similar results. Responding for MDMA was generally low with an average of 3 – 4 responses per session and only 63% of animals maintained responding for MDMA at rates significantly greater than saline (Ratzenboeck, Saria, Kriechbaum, & Zernig, 2001). Other studies have found similar low rates of responding, that is, 2 – 7 responses per session (De La Garza, Fabrizio, & Gupta, 2007; Reveron, Maier, & Duvauchelle, 2006). This led to suggestions that MDMA was not a very efficacious reinforcer (Beardsley et al., 1986; Lamb & Griffiths, 1987; Ratzenboeck et al., 2001).

Other studies have reported much higher levels of responding, however (Braida & Sala, 2002; Cornish et al., 2003; Dalley et al., 2007; Daniela, Brennan, Gittings, Hely, & Schenk, 2004; Schenk, Gittings, Johnstone, & Daniela, 2003). These mixed findings might be explained by differences in methodology. For example, in the study conducted by Ratzenbroeck and colleagues (2001), there were up to four sessions a day alternating with cocaine and saline self-administration. The lack of repeated discrete trials coupled with the relatively long half-life of MDMA may not have engendered optimal operant learning (Griffiths, Brady, & Bradford, 1979). Longer infusions times and shorter / lack of time out scheduling may also have contributed to higher rates of MDMA self-administration in

these studies (De La Garza et al., 2007). Nonetheless, a number of recent studies have reported reliable MDMA self-administration (Aarde, Miller, Creehan, Vandewater, & Taffe, 2015; Ball & Slane, 2012, 2014; Ball et al., 2015; Ball, Walsh, & Rebec, 2007; Bird & Schenk, 2013; Bradbury et al., 2013; Colussi-Mas, Wise, Howard, & Schenk, 2010; Creehan, Vandewater, & Taffe, 2015; Do & Schenk, 2013; Feduccia, Kongovi, & Duvauchelle, 2010; Gould et al., 2011; Kivell, Day, Bosch, Schenk, & Miller, 2010; Oakly, Brox, Schenk, & Ellenbroek, 2013; Reveron, Maier, & Duvauchelle, 2010; Schenk & Bradbury, 2015; Schenk et al., 2007; Z. Wang & Woolverton, 2007).

Once acquired, MDMA self-administration is comparable to the self-administration of other drugs of abuse. MDMA self-administration produced an inverted U-shaped dose effect curve (Daniela et al., 2004; Ratzenboeck et al., 2001; Schenk et al., 2003). When the infusion dose was halved, the number of responses doubled in order to keep the intake of drug constant (Do & Schenk, 2013; Reveron et al., 2010; Schenk et al., 2012). Likewise, an increase the FR response requirement resulted in the proportional increase in lever pressing (Daniela, Gittings, & Schenk, 2006; Schenk, Gittings, & Colussi-Mas, 2011). Replacing MDMA with its vehicle solution resulted in extinction of the operant behaviour that was subsequently reinstated by reintroduction of the drug (Daniela et al., 2006; Schenk et al., 2011). Further, extinguished drug seeking behaviour following MDMA self-administration was reinstated by priming injections of MDMA, cocaine, or yohimbine (stress inducer), and by the presentation of a light stimulus previously paired with MDMA infusions (Ball et al., 2015, 2007; Schenk et al., 2011; Schenk, Hely, Gittings, Lake, & Daniela, 2008).

The acquisition of MDMA self-administration, however, exhibits a profile that differs from that of other drugs of abuse. Firstly, acquisition of MDMA self-administration proceeds with a protracted time course, with low rates of responding during initial test sessions (Schenk et al., 2012). Acquisition of MDMA self-administration typically requires around 15 daily sessions (Schenk et al., 2012) whereas cocaine or amphetamine self-administration is usually acquired within a few days (Carroll & Lac, 1997). A more striking difference is that only about 50% of rats meet acquisition criteria for MDMA self-administration (Schenk et al., 2012) whereas virtually all animals acquire cocaine or amphetamine self-administration (Carroll & Lac, 1997). These differences may reflect the unique pharmacology of MDMA compared to other psychostimulant drugs of abuse.

Pharmacology of MDMA

MDMA is a ring-substituted phenethylamine, being structurally similar to methamphetamine (psychostimulant) and mescaline (hallucinogen). It is a potent indirect agonist of the monoamine neurotransmitters: serotonin (5-HT), dopamine (DA), and noradrenaline (NA). This is accomplished by competitive binding to the monoamine transporters, which prevents the reuptake of monoamines increasing synaptic concentrations of 5-HT, DA, and NA (Battaglia, Brooks, Kulsakdinun, & De Souza, 1988; Berger, Gu, & Azmitia, 1992; Cleary & Docherty, 2003; Cole & Sumnall, 2003; J. L. Fitzgerald & Reid, 1990; Hekmatpanah & Peroutka, 1990; Hysek et al., 2011; Iravani, Asari, Patel, Wieczorek, & Kruk, 2000; Nash & Brodkin, 1991; Rudnick & Wall, 1992). Acting as a substrate for the monoamine transporters, MDMA also enters the neuron and interacts with the vesicular monoamine transporter 2 (VMAT-2), preventing the repackaging of cytosolic monoamines into vesicles whilst displacing monoamines from the vesicles into the cytosol (Bogen, Haug, Myhre, & Fonnum, 2003; Eiden & Weihe, 2011; J. L. Fitzgerald & Reid, 1990; Fleckenstein et al., 2002; Gu & Azmitia, 1993; Rudnick & Wall, 1992; Sabol & Seiden, 1998; Schuldiner, Steiner-Mordoch, Yelin, Wall, & Rudnick, 1993; Sulzer & Rayport, 1990). Transporter reversal then results in the substantial efflux of cytosolic monoamines into the synapse (Crespi, Mennini, & Gobbi, 1997; Gudelsky & Nash, 2002; Rudnick & Wall, 1992). Because MDMA has an affinity for the 5-HT transporter several fold higher than the NA or the DA transporter, these effects are predominantly exerted on the 5-HT system (Battaglia, Brooks, et al., 1988).

MDMA further potentiates its effects on the monoamine system by inhibiting monoamine oxidase (MAO), the enzyme that metabolises 5-HT, DA, and NA in the cytosol and extracellular space (Dworkin, Guerin, Co, Smith, & Goeders, 1988; Leonardi & Azmitia, 1994; Scorza et al., 1997). Moreover, MDMA may induce carrier-independent, Ca+ dependent, release of neurotransmitters via exocytosis (Crespi et al., 1997; Hondebrink, Meulenbelt, Meijer, van den Berg, & Westerink, 2011; Maura, Gemignani, Versace, Martire, & Raiteri, 1982; Nagayasu, Kitaichi, Shirakawa, Nakagawa, & Kaneko, 2010). MDMA also induces the release of acetylcholine and has affinities for a range of brain receptors including the, 5-HT_1 and 5-HT_2 receptors, D_1- and D_2-like receptors, α1-, α2-, and β2-adrenergic receptors, as well as muscarinic and histamine receptors (Battaglia, Brooks, et al., 1988).

Measurement of synaptic concentrations of neurotransmitters using *in vivo* microdialysis has revealed that MDMA stimulates the release of 5-HT to a far greater extent than any other neurotransmitters (see Green, Mechan, Elliott, O'Shea, & Colado, 2003; Gudelsky & Yamamoto, 2008). For example, Bauman and colleagues measured synaptic concentrations of 5-HT and DA in the nucleus accumbens (NAcc), caudate nucleus, and prefrontal cortex (PFC) following a range of MDMA doses in rats. The increase in synaptic 5-HT was 2 – 6 times greater than the increase in DA, depending on brain region and dose, although the lowest dose of MDMA (1 mg/kg) failed to significantly increase synaptic NAcc DA at all (Baumann, Clark, Franken, Rutter, & Rothman, 2008; Baumann, Clark, & Rothman, 2008; Baumann et al., 2005). The highest dose (7.5 mg/kg) increased 5-HT and DA concentrations in the NAcc by 3000% and 500%, respectively (Baumann, Clark, Franken, et al., 2008). As will be discussed in the next section, this is not a pharmacological profile typical of drugs of abuse.

Pharmacology of self-administration

In all animals, including humans, natural rewards such as food or sex produce an increase in activity of the neurotransmitter, DA, particularly within the NAcc (Bassareo & Di Chiara, 1999a, 1999b; Fiorino, Coury, & Phillips, 1997; Pfaus, Mendelson, & Phillips, 1990; Pfaus & Phillips, 1991; Schott et al., 2008; Schultz, Apicella, & Ljungberg, 1993). The NAcc receives DAergic input via the medial forebrain bundle from the ventral tegmental area (VTA; Oades & Halliday, 1987). The VTA is the origin of DA cell bodies that also project to the amygdala and PFC (Oades & Halliday, 1987). Drugs of abuse similarly act upon these DAergic pathways, often to a much greater extent than natural rewards (Di Chiara & Imperato, 1988). A wealth of evidence indicates that DA activity within these systems plays a pivotal in the reinforcing effects of drugs of abuse and their self-administration by laboratory animals (Koob, 1992; Pierce & Kumaresan, 2006).

Firstly, all drugs of abuse share the capacity to increase synaptic concentrations of mesoaccumbal DA. Di Chiara and Imperato (1988) measured extracellular DA concentrations in freely moving rats after the administration of various drugs. Drugs that are abused such as amphetamine, cocaine, nicotine, and morphine, increased synaptic DA in the nucleus accumbens by up to 1000%, 330%, 225%, and 200%, respectively (Di Chiara & Imperato, 1988). Drugs that are not abused such as imipramine (anti-depressant), atropine (anti-muscarinic drug), and diphenhydramine (anti-histamine), did not increase synaptic DA concentration (Di Chiara & Imperato, 1988). This increase in synaptic DA

produced by drugs of abuse is directly related to the pattern of responding during self-administration. Laboratory animals initially responded rapidly, greatly increasing extracellular dopamine levels; after this initial peak, DA levels were maintained at an elevated level for the duration of the session with sustained pressing (Hurd, Weiss, Koob, And, & Ungerstedt, 1989; Pettit & Justice, 1991; Ranaldi, Pocock, Zereik, & Wise, 1999; R. A. Wise et al., 1995).

Secondly, drugs that selectively facilitate DA neurotransmission are self-administered. Substitution of cocaine or amphetamine with selective DA agonists continues to maintain self-administration behaviour (Ranaldi, Wang, & Woolverton, 2001; Weed & Woolverton, 1995; Woolverton, Goldberg, & Ginos, 1984). Moreover, selective DA agonists alone are often readily self-administered by naïve animals (Howell & Byrd, 1991; Nader & Mach, 1996; Self, Belluzzi, Kossuth, & Stein, 1996; Self & Stein, 1992; Weed & Woolverton, 1995; Yokel & Wise, 1978).

Thirdly, pharmacological manipulation of the DA system influences self-administration. Administration of DA agonists decreases self-administration of cocaine, amphetamine, or methamphetamine, producing a leftward shift in the dose effect curve (Barrett, Miller, Dohrmann, & Caine, 2004; Caine & Koob, 1994a; Munzar, Baumann, Shoaib, & Goldberg, 1999; Yokel & Wise, 1978). This compensatory responding is similar to what is seen when the self-administration infusion dose is increased (Goldberg, Hoffmeister, et al., 1971; Pickens & Harris, 1968; Weeks & Collins, 1964). Conversely, administration of DA antagonists produces a rightward shift in the dose effect curve for cocaine or amphetamine self-administration, represented by an increase in responding (Britton et al., 1991; Caine & Koob, 1994a; Corrigall & Coen, 1991a; Hubner & Edward Moreton, 1991; Koob, Le, & Creese, 1987; Phillips, Robbins, & Everitt, 1994; Risner & Jones, 1976; Yokel & Wise, 1976); similar to what is seen when the self-administration infusion dose is decreased (Goldberg, Hoffmeister, et al., 1971; Pickens & Harris, 1968; Weeks & Collins, 1964).

Finally, destruction of dopamine nerve terminals in the mesoaccumbal DA system decreases drug self-administration. Lesions of the NAcc and the VTA with 6-hydroxydopamine (6-OHDA) produced a long-lasting decrease in the self-administration of cocaine (Caine & Koob, 1994b; Roberts, Corcoran, & Fibiger, 1977; Roberts, Koob, Klonoff, & Fibiger, 1980; Roberts & Koob, 1982). The recovery of cocaine self-administration was correlated with the level of DA depletion produced by the lesion; rats

with the greatest depletion of DA failed to recover cocaine self-administration at all (Roberts et al., 1980; Roberts & Koob, 1982). Lesions with 6-OHDA in the NAcc also produced long-lasting reductions in the self-administration of nicotine and amphetamine (Corrigall & Coen, 1991b; Lyness, Friedle, & Moore, 1979; Singer, Wallace, & Hall, 1982). Further, the acquisition of amphetamine (Lyness et al., 1979) and heroin (Bozarth & Wise, 1986) self-administration was prevented by 6-OHDA lesions of the NAcc and VTA, respectively.

In contrast to the role of DA, several lines of evidence indicate that 5-HT is inhibitory to the self-administration of drugs of abuse. Selective 5-HT agonists are not abused by humans nor are they self-administered by laboratory animals (Götestam & Andersson, 1975; Howell & Byrd, 1995; Roberts et al., 1999; Tessel & Woods, 1975; Vanover, Nader, & Woolverton, 1992). Roberts and colleagues tested various cocaine analogues that had a range of affinities for the DA and 5-HT transporters in self-administration. They found that drugs with a higher affinity ratio for the DA transporter over the 5-HT transporter were more likely to be self-administered (Roberts et al., 1999). Similarly, Wee and colleagues tested a number of amphetamine analogues with similar potencies as in-vivo releasers of DA but differed in their potency for 5-HT release. They found that greater self-administration responding correlated with lower 5-HT release (Wee et al., 2005). *d*-amphetamine was the most readily self-administered drug and had a potency as a releaser of DA 220 times greater than 5-HT (Wee et al., 2005).

Administration of various serotonin agonists decreased self-administration of amphetamine (Dianna, Smith, Smith, & Lyness, 1986; Porrino et al., 1989; Wee & Woolverton, 2006), methamphetamine (Munzar et al., 1999), cocaine (Carroll, Lac, Asencio, & Kragh, 1990a, 1990b; Czoty, Ginsburg, & Howell, 2002; Peltier & Schenk, 1993; Richardson & Roberts, 1991), ethanol (Lyness & Smith, 1992), and heroin (Higgins, Wang, Corrigall, & Sellers, 1994; Y. Wang, Joharchi, Fletcher, Sellers, & Higgins, 1995). Wee and Woolverton (2006) mixed the 5-HT agonist, fenfluramine, with amphetamine at various doses and found that a higher ratio of fenfluramine:amphetamine, (i.e. 5-HT:DA release) was negatively correlated with self-administration responding. Increasing 5-HT levels by the administration of L-tryptophan, the amino acid precursor of 5-HT, decreased self-administration of cocaine (Carroll et al., 1990b; McGregor, Lacosta, & Roberts, 1993) and amphetamine (Lyness, 1983; Smith, Dianna, Smith, Leccese, & Lyness, 1986). Conversely, 5-HT depletion achieved by 5, 7-dihydroxytryptamine (5, 7-DHT) lesions or

pre-treatment with the 5-HT synthesis inhibitor, p-chlorophenylalanine (pCPA), facilitated self-administration of ethanol (Lyness & Smith, 1992), amphetamine (Fletcher, Korth, & Chambers, 1999; Leccese & Lyness, 1984; Lyness, Friedle, & Moore, 1980), MDMA (Bradbury et al., 2013), and morphine (Dworkin et al., 1988; Smith, Shultz, Co, Goeders, & Dworkin, 1987).

5-HT projections originating from the dorsal and median raphe innervate virtually all parts of the central nervous system including the VTA, NAcc, and PFC (Di Matteo, Di Giovanni, Pierucci, & Esposito, 2008). 5-HTergic mechanisms can modulate DA neurotransmission within these structures by direct activation of 5-HT receptors located on DA neurons or via inhibitory-GABA and excitatory-glutamate mediated connections (Bankson & Cunningham, 2001; Di Matteo et al., 2008; Gudelsky & Yamamoto, 2008). Increasing extracellular 5-HT concentrations with a selective serotonin reuptake inhibitor (SSRI), administered at doses that decreased cocaine self-administration, also decreased cocaine-produced synaptic DA in the caudate nucleus (Czoty et al., 2002). Thus, it was suggested that the inhibitory effect of 5-HT on cocaine self-administration was due to its inhibitory effect on DA neurotransmission (Czoty et al., 2002). The relationship between 5-HT and DA is complicated, however, as activation of several 5-HT receptors such as the 5-HT_{1a}, 5-HT_{1b}, 5-HT_{2a}, 5-HT_{2b}, facilitate DA release whereas activation of the 5-HT_{2c} receptor mediates an inhibitory effect on DA release (Reviewed by Di Matteo et al., 2008).

It is evident that DA neurotransmission underlies the reinforcing effects of drugs of abuse and their self-administration by laboratory animals. In contrast, increased 5-HT neurotransmission appears to be inhibitory to the self-administration of drugs of abuse. Acute administration of MDMA increases synaptic concentrations of 5-HT to a far greater extent than DA (Green et al., 2003). Why then, is MDMA self-administered by non-human primates (Beardsley et al., 1986; Lamb & Griffiths, 1987), rats (Schenk, 2009), and mice (Trigo, Panayi, Soria, Maldonado, & Robledo, 2006), and why is it abused by humans (Cottler et al., 2009)?

Neurochemical consequences of repeated MDMA exposure

The answer to this question lies in an understanding of the changes in 5-HTergic and DAergic mechanisms that occur with repeated exposure to MDMA. Since the late 1980's, several studies have reported deficits in 5-HT neurotransmission following repeated MDMA exposure. Repeated experimenter-administered injections of MDMA (10 – 40 mg/kg, twice daily, for 4 days) produced dose-dependant reductions in rat brain 5-HT

(Battaglia, Yeh, & De Souza, 1988; Commins et al., 1987; O'Hearn, Battaglia, De Souza, Kuhar, & Molliver, 1988), 5-HIAA (Battaglia, Yeh, et al., 1988; Battaglia et al., 1987), and decreased 5-HT uptake sites (Battaglia, Yeh, et al., 1988; Battaglia et al., 1987; Commins et al., 1987). Synaptic overflow of striatal 5-HT was also diminished following repeated MDMA exposure (10 mg/kg × 4; Shankaran & Gudelsky, 1999). Even single injections of MDMA (10 – 40 mg/kg) produced reductions in rat brain 5-HT (Mokler, Robinson, & Rosecrans, 1987; Schmidt, 1987; Stone, Merchant, Hanson, & Gibb, 1987), 5-HIAA (Mokler et al., 1987; Stone et al., 1987), tryptophan hydroxylase activity (Stone et al., 1987), and 5-HT uptake sites (Schmidt, 1987). These effects appear to be due to the extreme effect of MDMA on the 5-HT system since co-administration of the SSRIs, citalopram (Battaglia, Yeh, et al., 1988), or fluoxetine (Schmidt, 1987) prevented the development of 5-HTergic deficits. Following repeated MDMA exposure, 5-HT deficits have also been demonstrated in guinea pigs (Commins et al., 1987), non-human primates (Insel, Battaglia, Johannessen, Marra, & De Souza, 1989; Kleven, Woolverton, & Seiden, 1989; Ricaurte, DeLanney, Irwin, & Langston, 1988; Wilson, Ricaurte, & Molliver, 1989), and even humans (McCann, Ridenour, Shaham, & Ricaurte, 1994; McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998; Semple, Ebmeier, Glabus, O'Carroll, & Johnstone, 1999; Ralph Thomasius et al., 2003; Verkes et al., 2001). In rats, these 5-HTergic deficits take several months to fully recover (Battaglia, Yeh, et al., 1988; Scanzello, Hatzidimitriou, Martello, Katz, & Ricaurte, 1993) whereas in non-human primates and humans, 5-HT deficits last for several years (Ricaurte, Martello, Katz, & Martello, 1992; R. Thomasius et al., 2006).

The use of relatively high doses of non-contingent MDMA has have led to some controversy over the relevance of these findings for human MDMA use (see Baumann, Wang, & Rothman, 2007; de la Torre & Farré, 2004; Ricaurte, McCann, Szabo, & Scheffel, 2000). Studies investigating 5-HTergic deficits following self-administered MDMA offer better external validity. Lower densities of 5-HT uptake sites (Schenk et al., 2007) and decreased 5-HT tissue levels (Do & Schenk, 2013) were found in MDMA self-administering rats. Tissue levels had decreased by ~35% two weeks following cessation of self-administration but had recovered by ten weeks (Do & Schenk, 2013). MDMA-produced synaptic overflow of NAcc 5-HT was also decreased following 20 days of MDMA self-administration (Reveron et al., 2010). Deficits appear to be dependent on exposure levels, however, as self-administration of smaller amounts of MDMA failed to

significantly decrease 5-HT tissue levels or 5-HT uptake sites in rats (Do & Schenk, 2013) or rhesus monkeys (Banks et al., 2008; Fantegrossi et al., 2004).

While a considerable amount of evidence indicates that 5-HT neurotransmission decreases with repeated MDMA exposure, some studies have found that repeated MDMA exposure enhanced DAergic activity. Tissue levels of DA were increased four weeks after repeated MDMA exposure (Mayerhofer, Kovar, & Schmidt, 2001). The capacity for MDMA (Kalivas, Duffy, & White, 1998) and cocaine (Morgan, Horan, Dewey, & Ashby Jr., 1997) to produce increases in NAcc DA was significantly enhanced for rats previously treated MDMA (20 mg/kg × 4, over 4 days). Intermittent dosing appears critical to the development of this sensitised DAergic response, however, as when 40 mg/kg was administered over a single day there were no changes (Shankaran & Gudelsky, 1999). MDMA-(10 mg/kg) produced synaptic striatal DA was significantly increased for rats that met an acquisition criteria for MDMA self-administration (Colussi-Mas et al., 2010). Following the self-administration of a lower amount of MDMA, however (average of ~100 mg/kg compared to 165 mg/kg in the former study), synaptic NAcc DA produced by a self-administered infusion of MDMA (3 mg/kg) was unchanged (Reveron et al., 2010).

Implications for MDMA self-administration. As with other drugs of abuse, increased 5-HT neurotransmission is inhibitory to the reinforcing effects of MDMA. Rats with a greater NAcc 5-HT response to MDMA were less likely to subsequently acquire MDMA self-administration (Bradbury et al., 2013). It is not surprising, then, that manipulations that decreased MDMA-stimulated 5-HT increased the reinforcing effects of MDMA. Both neurotoxic 5-7 DHT lesions (Bradbury et al., 2013) and a genetic mutation of the 5-HT transporter (Oakly et al., 2013) decreased the latency to acquire MDMA self-administration and increased the percentage of rats that met acquisition criteria; rendering the acquisition profile of MDMA self-administration more comparable to other psychostimulant drugs of abuse. These findings suggest that MDMA-produced increases in 5-HT limits the acquisition of MDMA self-administration.

Although MDMA preferentially facilities 5-HT neurotransmission, evidence suggests that the reinforcing effects of MDMA, as with other drugs of abuse, are mediated by DAergic mechanisms. S(+)-MDMA, the more potent DA releasing isomer of MDMA, was more readily self-administered by rhesus monkeys than R(-)-MDMA, the less potent DA releasing isomer; racemic (±)-MDMA fell in between the two enantiomers (Johnson, Hoffman, & Nichols, 1986; Z. Wang & Woolverton, 2007). In rats, treatment with DA

receptor antagonists produced a rightward shift in the dose-response curve for MDMA self-administration (Brennan, Carati, Lea, Fitzmaurice, & Schenk, 2009; Daniela et al., 2004). Perhaps the most compelling piece of evidence is that rats that met an acquisition criteria for MDMA self-administration displayed greater MDMA-produced synaptic striatal DA compared to rats that failed to acquire (Colussi-Mas et al., 2010). This suggests that the development of a sensitised DAergic response might be critical to the acquisition of MDMA self-administration.

Our working hypothesis is that repeated MDMA exposure results in 5-HTergic deficits and DA sensitisation, neuroadaptations that, for the reasons discussed above, would be expected to enhance the reinforcing efficacy of MDMA. These neuroadaptations facilitate the eventual acquisition of self-administration of MDMA, contributing to the progressive escalation of MDMA intake, which in turn, leads to further neuroadaptations, and so on (Schenk, 2011). Thus, with repeated exposure, the pharmacological profile of MDMA begins to become more similar to other drugs of abuse such as amphetamine or cocaine. The influence of 5-HTergic mechanisms on the acquisition of MDMA self-administration has already received some attention (see above). The influence of DAergic mechanisms, however, is less understood and was the premise for the present thesis.

Behavioural sensitisation

One way to investigate the neuroadaptations produced by repeated drug exposure is to study the corresponding changes in behaviour. Some drug-produced behaviours may decrease (become tolerant) whereas other behaviours can increase (beceome sensitised; Stewart & Badiani, 1993). The latter phenomenon was first reported in the 1930's (Downs & Eddy, 1932a, 1932b; Seevers & Tatum, 1931) and refers to the progressive and persistent increase in drug-produced behaviour that occurs with repeated exposure to some drugs. Sensitisation of several behaviours including sniffing, head movements, and rearing have been reported in rats although the most commonly measured behaviour is locomotor activity (Pierce & Kalivas, 1997; Post & Rose, 1976; Robinson, 1984; Stewart & Badiani, 1993).

Behavioural sensitisation is characterised by two phases: the development of sensitisation and the expression of sensitisation. The development of sensitisation (also called the initiation, or induction of sensitisation) typically involves a regimen of repeated intermittent drug exposure followed by a withdrawal period of at least one day (Pierce & Kalivas, 1997). However, in some cases even a single injection has been sufficient to

induce sensitisation (Vanderschuren, Schmidt, et al., 1999). The expression of sensitisation refers to the manifestation of the sensitised behavioural response produced by the subsequent re-exposure to the drug (Pierce & Kalivas, 1997). A greater behavioural response in drug treated animals compared to vehicle treated controls indicates the development of a sensitised response (i.e. a leftward shift in the dose response curve).

Behavioural sensitisation has been observed following repeated administration of several different psychostimulants including amphetamine, cocaine, methylphenidate, and MDMA, as well as other types of drugs including opioids, nicotine, and ethanol (for reviews see Kalivas & Stewart, 1991; Pierce & Kalivas, 1997; Robinson & Becker, 1986; Vanderschuren & Kalivas, 2000). Repeated exposure to some drugs can also result in cross-sensitisation to the behavioural effects of other drugs, suggesting the involvement of similar neural systems (Kalivas & Stewart, 1991; Pierce & Kalivas, 1997; Robinson & Becker, 1986; Vanderschuren & Kalivas, 2000).

The relationship between central DAergic neurotransmission and motor activity has long been known (Carlsson, Lindqvist, Magnusson, & Waldeck, 1958; Costall & Naylor, 1979; Hornykiewicz, 1966; Ungerstedt, 1979). The capacity of a drug to produce locomotor hyperactivity is dependent on its capacity to facilitate DA neurotransmission; drugs with a greater effect on DA generally produce a greater effect on locomotor activity (Hurd et al., 1989; Steinpreis & Salamone, 1993). It is not surprising, then, that sensitisation of locomotor activity is mirrored by the sensitisation of central DAergic mechanisms (Kalivas & Stewart, 1991; Pierce & Kalivas, 1997; Vanderschuren & Kalivas, 2000). Behavioural sensitisation has, therefore, often been used to investigate changes in DAergic functioning produced by repeated drug exposure (see Kalivas & Stewart, 1991; Vanderschuren & Kalivas, 2000).

Sensitisation and the acquisition of self-administration

The DAergic neuroadaptations underlying behavioural sensitisation have been proposed to underlie several aspects of addiction. One function of the central DAergic system is to attribute incentive salience to stimuli, imbuing them with salience and making them ‘wanted’ (Berridge & Robinson, 1998; Robinson & Berridge, 1993; Roy A Wise, 2004). The incentive-sensitisation theory of addiction suggests that repeated use of addictive drugs leads to the sensitisation of this neural system which renderers some individuals hypersensitive to the drug, the act of drug taking, and drug associated stimuli (Robinson & Berridge, 1993). Thus, it is the sensitisation of incentive salience towards

drugs and drug-related stimuli that transforms ordinary 'wanting' into excessive drug craving (Robinson & Berridge, 1993). Given that sensitised central DAergic mechanisms have been implicated in the compulsive drug-taking and drug-seeking behaviour characteristic of addiction, sensitisation has been extensively studied in the context of self-administration.

The acquisition of self-administration of many drugs is dose-dependent; self-administration of higher doses is typically acquired with a shorter latency than when lower doses serve as the reinforcer (Carroll & Lac, 1997; Schenk et al., 1993). Much like increasing the dose, exposing animals to a sensitising pre-treatment regimen of drug exposure shifts the acquisition curve for self-administration to the left (sensitisation). Low doses of amphetamine and cocaine, that were normally subthreshold as a reinforcer, were reliably self-administered in rats pre-treated with amphetamine (Piazza et al., 1991; Piazza, Deminiere, le Moal, & Simon, 1990; Piazza, Deminière, Le Moal, & Simon, 1989; Pierre & Vezina, 1997; Vezina, Lorrain, Arnold, Austin, & Suto, 2002) or cocaine, (Horger, Shelton, & Schenk, 1990; Zhao & Becker, 2010), respectively. When higher doses are used, acquisition of self-administration amphetamine does not appear to be influenced by prior exposure (Lorrain, Arnold, & Vezina, 2000; Mendrek, Blaha, & Phillips, 1998). However, because virtually all rats acquire self-administration of higher doses of amphetamine within a few days, a ceiling effect would likely conceal a significant finding. Indeed, when tested under a progressive ratio schedule, where the fixed ratio required to earn an infusion progressively increases, rats pre-treated with amphetamine worked harder in order to obtain an infusion suggesting an increase in the reinforcing efficacy of amphetamine (Lorrain et al., 2000; Mendrek et al., 1998; Vezina et al., 2002). Pre-treatment with ethanol has been shown to facilitate the subsequent acquisition of ethanol self-administration (Camarini & Hodge, 2004; Rodd-Henricks et al., 2002). Further, repeated exposure to amphetamine, MDMA, caffeine, and nicotine, facilitated the acquisition of cocaine self-administration indicating cross-sensitisation (Fletcher, Robinson, & Slippoy, 2001; Horger, Giles, & Schenk, 1992; Horger, Wellman, Morien, Davies, & Schenk, 1991; Valadez & Schenk, 1994).

Evidence suggests that the same sensitised DAergic mechanisms underlying behavioural sensitisation are implicated in the sensitised acquisition of self-administration (Vezina, 2004). Firstly, only pre-treatment regimens that result in behavioural / DAergic sensitisation facilitated subsequent self-administration. For example, repeated

administration of amphetamine systemically or directly into the VTA produced behavioural and DAergic sensitisation (Cador, Bjijou, & Stinus, 1995; Kalivas & Weber, 1988; Vezina, 1993) and facilitated subsequent amphetamine self-administration (Vezina et al., 2002). Repeated amphetamine administration directly into the NAcc, however, did not result in sensitisation (Cador et al., 1995; Kalivas & Weber, 1988) nor did it facilitate subsequent drug-taking (Vezina et al., 2002). Secondly, procedures that prevent the development of behavioural and DAegric sensitisation also prevent the subsequent facilitation of drug taking. For example, treatment with a D_1 antagonist blocked the development of amphetamine sensitisation (Vezina & Stewart, 1989; Vezina, 1996) and blocked the subsequent facilitation of self-administration (Pierre & Vezina, 1998).

The present thesis

Acute behavioural effects of MDMA. As with many other drugs of abuse, acute administration of MDMA produces dose-dependent increases in locomotor hyperactivity (Brennan & Schenk, 2006; Gold, Koob, & Geyer, 1988; Spanos & Yamamoto, 1989) by virtue of the drug's effects on DA neurotransmission. MDMA-produced hyperactivity was mirrored by increased synaptic overflow of DA (Baumann, Clark, & Rothman, 2008) and was attenuated following 6-OHDA lesions (Gold, Hubner, & Koob, 1989). Moreover, administration of D_1 and D_2 antagonists dose-dependently attenuated MDMA-produced locomotor activity (Brennan et al., 2009; Bubar, Pack, Frankel, & Cunningham, 2004; Daniela et al., 2004), an effect that correlated with attenuated firing of striatal motor neurons (Ball, Budreau, & Rebec, 2003).

MDMA-produced increases in 5-HT neurotransmission also influence MDMA-produced hyperactivity. 5-HT depletion achieved through 5, 7-DHT lesions or pCPA administration decreased MDMA-produced locomotion (Callaway, Wing, & Geyer, 1990; Kehne et al., 1996). Administration of 5-HT_{1a} (Callaway, Rempel, Peng, & Geyer, 1992; Kehne et al., 1996; McCreary, Bankson, & Cunningham, 1999) and 5-HT_{2a} (Ball & Rebec, 2005; Herin, Liu, Ullrich, Rice, & Cunningham, 2005; Kehne et al., 1996) antagonists attenuated MDMA-produced locomotion whereas 5-HT_{2c} (Bankson & Cunningham, 2002; Fletcher, Sinyard, & Higgins, 2006; Gold & Koob, 1988) antagonists potentiated MDMA-produced locomotion. With many 5-HT receptors influencing DA neurotransmission (Di Matteo et al., 2008), MDMA-produced increases in 5-HT may contribute to MDMA-produced hyperactivity via interactions between these two neurotransmitter systems (Ball & Rebec, 2005; Bankson & Cunningham, 2001).

The pattern of hyperactivity produced by MDMA differs from that of other psychostimulants in that it is typically restricted to the periphery of a closed chamber (Bradbury, Gittings, & Schenk, 2012; Gold et al., 1988; Ludwig, Mihov, & Schwarting, 2008; McCreary et al., 1999; Palenicek, Votava, Bubenikova, & Horacek, 2005). In contrast, drugs that preferentially facilitate DA neurotransmission such as amphetamine produce activity that is more generally distributed over the entire chamber (Bradbury et al., 2012; Geyer, Russo, & Masten, 1986; Gold, Koob, & Geyer, 1990). It has been suggested that the thigmotaxic response produced by MDMA is due the preferential effect of MDMA on 5-HT neurotransmission (Gold & Koob, 1988).

While horizontal locomotion is increased by MDMA administration, vertical locomotion (i.e. rearing activity) is generally suppressed by MDMA (Callaway et al., 1990; Fone et al., 2002; Kehne et al., 1996; Ludwig et al., 2008; Sadananda, Natusch, Karrenbauer, & Schwarting, 2012; M. R. Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007). Gold and colleagues, however, found that although MDMA attenuated rearing during the initial 30 min, the highest dose of MDMA (10 mg/kg) potentiated rearing 90 min following MDMA administration (Gold et al., 1988).

Relatively fewer studies have investigated the neurochemical underpinnings of rearing activity compared to horizontal locomotion, although evidences suggests that increased DAergic activity also underlies rearing activity. Basal rearing activity was attenuated by a D_1 antagonist (Hoffman & Beninger, 1985). DA injected into the NAcc produced rearing activity, which was dose-dependently attenuated by the endogenous neuropeptide, neurotensin (Kalivas, Nemeroff, & Prange, 1984). Rearing activity that was produced by a D_1 agonist was blocked by D_1 and D_2 receptor antagonists (Molloy & Waddington, 1985). Further, decreasing extracellular DA in the NAcc via retrodialysis of nociceptin attenuated cocaine-produced rearing (Vazquez-DeRose et al., 2013). Interestingly, although racemic ±MDMA typically supressing rearing, S(+)-MDMA, the more potent DA releasing isomer, facilitated rearing (Bubar et al., 2004; Herin et al., 2005; McCreary et al., 1999), which suggests that increased DA plays a role in MDMA-produced rearing activity. Indeed, both D_1 and D_2 antagonists attenuated S(+)-MDMA-produced rearing activity (Bubar et al., 2004).

5-HT may also play a role in mediating rearing behaviour, possibly via interactions with DA neurons. Administration of 5-HT into the dorsal raphe attenuated rearing (Hillegaart, 1990). Administration of 5-HT_{1a} (Hillegaart, Estival, & Ahlenius, 1996;

Hillegaart, Wadenberg, & Ahlenius, 1989; Hillegaart, 1990; Sadananda et al., 2012) or 5-$HT_{2a/c}$ agonists (Hillegaart et al., 1996) also decreased rearing. MDMA-supressed rearing, however, was not affected by 5-HT_{2a} antagonists, haloperidol (nonselective D_2 antagonist), or SSRI treatment (Callaway et al., 1990; Kehne et al., 1996).

Experiment 1: MDMA-induced behavioural sensitisation. Repeated, intermittent, MDMA exposure can result in the sensitisation of these acute behavioural responses. Locomotor activity was enhanced following repeated experimenter- (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008; Kalivas et al., 1998; Spanos & Yamamoto, 1989) and self-administered MDMA (Schenk & Bradbury, 2015). Locomotor activity in the centre of the activity chamber was specifically sensitised (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008; Ludwig et al., 2008; McCreary et al., 1999). Following repeated experimenter- (Ludwig et al., 2008) and self-administered (Schenk & Bradbury, 2015) MDMA, rearing activity produced by MDMA was also increased.

As with other drugs of abuse, DAergic mechanisms appear to play an important role in MDMA sensitisation. Repeated MDMA exposure that produced behavioural sensitisation was accompanied by sensitised DAergic responses in the NAcc (Kalivas et al., 1998) and changes in accumbal c-Fos expression (Colussi-Mas & Schenk, 2008). Moreover, repeated MDMA exposure resulted in cross sensitisation to other, more potent, DAergic drugs including amphetamine, and cocaine (Bradbury et al., 2012; Kalivas et al., 1998). Little is known about the specific DA receptor mechanisms involved in MDMA sensitisation, however.

There are two families of DA receptors: D_1-like receptors, which include the D_1 and D_5 receptors, and D_2-like receptors, which include the D_2, D_3, and D_4 receptors (Missale, Nash, Robinson, Jaber, & Caron, 1998). These two families of DA receptors differ in their physiological functioning (Kebabian & Calne, 1979). D_1-like receptors are coupled to the G protein, G_s, which subsequently activates adenylyl cyclase, facilitating cyclic adenosine monophosphate (cAMP) activity (Missale et al., 1998). In contrast, D2-like receptors are coupled to G_i, which inhibits adenylyl cyclase and thus inhibits cAMP activity (Missale et al., 1998). Further, D_2 receptors can function as post-synaptic receptors (genetically long isoform) but also as auto-receptors (genetically short isoform), which modulate DA synthesis and release (Beaulieu & Gainetdinov, 2011).

The D_1 antagonist, SCH-23390, failed to block the development of MDMA sensitisation but blocked the expression when administered systemically or when injected

directly into the NAcc (Ramos, Goñi-Allo, & Aguirre, 2004). The expression of MDMA sensitisation was also blocked when SCH-23390 was injected into the medial PFC, however, the authors concluded this effect was due to agonism of 5-HT_{2c} receptors (Ramos, Goñi-Allo, & Aguirre, 2005), of which SCH-23390 has fairly good affinity (Briggs et al., 1991; Millan, Newman-Tancredi, Quentric, & Cussac, 2001). We have previously shown that repeated MDMA exposure produced cross-sensitisation to the locomotor activating effects of the D_1 agonist, SKF-81297, and the $D_{2/3}$ agonist, quinpirole (Bradbury et al., 2012). Together, these findings suggest that both D_1 and D_2-like receptors are implicated in the expression of MDMA sensitisation but D_1 receptors are not critically involved in the development of MDMA sensitisation.

The first experiment of the present thesis will, therefore, investigate the contribution of D_2 receptors to the development of MDMA behavioural sensitisation. Locomotor (total, centre, and peripheral) and rearing activity will be measured during a five-day MDMA pre-treatment regimen previously shown to induce behavioural sensitisation and during the subsequent test for the expression of MDMA sensitisation following two days of withdrawal (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008). The effect of MDMA pre-treatment, with or without co-administration of the selective D_2 antagonist, eticlopride will be determined. It is hypothesised that eticlopride will block the development of MDMA-produced behavioural sensitisation.

Experiment 2: Acquisition of MDMA self-administration. We have previously suggested that the development of a sensitised DAergic response to MDMA is critical to the acquisition of reliable MDMA self-administration (Schenk, 2011). In support of this idea, rats that met acquisition criteria for MDMA self-administration displayed increased MDMA-produced synaptic striatal DA compared to rats that failed to acquire. Because behavioural sensitisation induced by repeated MDMA exposure was accompanied by enhanced MDMA-produced NAcc DA release (Kalivas et al., 1998), and the reinforcing effects of MDMA have been attributed to DAergic mechanisms (Brennan et al., 2009; Daniela et al., 2004), repeated MDMA exposure would also be expected to sensitise the reinforcing effects of MDMA. Thus, the second experiment of the present thesis will investigate the effect of a sensitising pre-treatment regimen of MDMA exposure on the subsequent acquisition of MDMA self-administration. If the development of a sensitised response to MDMA is a critical determinant of MDMA self-administration, then pre-

treatment would be expected to increase the percentage of rats that subsequently acquire MDMA self-administration.

Because the DAergic mechanisms underlying sensitisation to the locomotor activating and reinforcing effects of drugs of abuse are thought to be similar (Vezina, 2004), the contribution of D_2 receptor mechanisms will also be investigated. The effects of MDMA pre-treatment, with or without eticlopride, on the subsequent acquisition of MDMA self-administration will be determined. Manipulations that prevent the development of sensitisation to other drugs of abuse also typically prevent the subsequent facilitation of self-administration (Pierre & Vezina, 1998). Therefore, if eticlopride prevents the development of MDMA sensitisation (experiment 1), it is expected that it would also prevent the hypothesised facilitation of MDMA self-administration following MDMA pre-treatment.

High dose regimens of repeated MDMA exposure produce 5-HT deficits (Baumann et al., 2007), which would also be expected to facilitate the acquisition of MDMA self-administration (Bradbury et al., 2013; Oakly et al., 2013). Thus, in order to focus on DAergic sensitisation, the dosing regimen used in the present thesis will use relatively lower doses of MDMA that have previously been shown not to produce decreases in 5-HT tissue levels (Bradbury et al., 2012) but still produced reliable behavioural sensitisation (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008).

Method

Subjects

Male Sprague-Dawley rats were bred in the vivarium at Victoria University of Wellington and housed in groups of four until they weighed 280 – 300 g. Thereafter, rats were housed individually in polycarbonate hanging cages in a temperature- (19-21^{o}C) and humidity- (55%) controlled environment. Food and water were available *ad libitum* at all times except during testing. The housing colony was maintained on a 12 hour light/dark cycle (lights on at 0700) with testing conducted during the light portion of the cycle. All experimental protocols were approved by the Animal Ethics Committee of Victoria University of Wellington.

Surgery

For self-administration experiments, 280 – 300 g rats were housed individually for at least one week prior to being surgically implanted with intravenous (i.v.) catheters. Deep anaesthesia was produced by an intraperitoneal (i.p.) injection of a solution

combining ketamine (90.0 mg/kg, PhoenixPharm, Auckland, New Zealand) and xylazine (9.0 mg/kg, Provet, Palmerston North, New Zealand) followed by a subcutaneous (s.c.) injection of the anti-inflammatory analgesic, Carprofen (5 mg/kg, Pfizer Animal Health, Auckland, New Zealand). Lacrilube® was applied to both eyes to prevent corneal desiccation. The external jugular vein was isolated and tied of at its anterior end using sterile thread. A Silastic® catheter (0.51 mm I.D., 1.34 mm O.D.) was inserted, advanced posteriorly towards the atrium, and secured in place with sterile thread. The distal end of the catheter, fitted with a 2 cm piece of 22 gauge stainless steel tubing, was routed subcutaneously to an exposed part of the skull where it was fixed in place using four jewellers screws embedded in dental acrylic. Hartmann's solution (2 × 5 ml, s.c.) was administered post-surgery to restore electrolyte balance. Daily Carprofen injections (5.0 mg/kg, s.c.) were administered for two days following surgery and the catheter was flushed daily with 0.2 ml of sterile 0.9% saline solution containing heparin (30 IU/ml) and penicillin (250 000 IU/ml) to prevent blood coagulation and infection.

Apparatus

Locomotor activity was measured in clear Plexiglas chambers (Med Associated Inc, USA; model ENV-515) measuring 42 × 42 × 30 cm, set in sound-attenuating boxes. The chambers each contained two sets of 16 infra-red sensors spaced 2.5 cm apart producing a lattice of beams 1.7 cm above the floor of the chamber. The sequential interruption of three beams (the approximate size of the body of a rat) was recorded as one locomotor activity count. For data collection, the chambers were divided into two areas: the central zone was defined as the central 19 × 19 cm and the remaining area was defined as the periphery. Another series of beams spaced 2.5 cm apart, 15 cm above the floor of the chamber were used to record vertical activity (rearing). Any interruption of at least one of these beams was recorded as one rearing count. A white-noise generator was used to mask any outside noise. To control for olfactory confounds, chambers were washed with Virkon 'S' disinfectant (Southern Veterinary Supplies, NZ) after each session. All locomotor experiments were run in a temperature- (19-21^{o}C) and humidity- (55%) controlled dark room, except for a dim red light that was used to illuminate the room during drug administrations.

Self-administration testing was conducted in standard operant chambers equipped with two levers (Med Associated Inc, USA; model ENV-001). Responses on the active lever resulted in a 0.1 ml infusion of MDMA (1.0 or 0.5 mg/kg) delivered over a period of

12 seconds and the concurrent illumination of a light located above the lever. Responses on the inactive lever were recorded but produced no programmed consequence. A 20 ml syringe housed in a mechanical pump (Med Associated Inc, USA; model – PHM-100A) was connected through a swivel apparatus to a length of microbore tubing and attached to the i.v. catheter. Drug delivery and data acquisition were controlled by the Med PC software. Self-administration testing was conducted within a temperature- (19-21^{o}C) and humidity- (55%) controlled dark room.

Experiment 1: procedure

On each of five daily pre-treatment sessions, rats received eticlopride (0.0, 0.05, or 0.3 mg/kg i.p.) and were immediately placed into the activity chambers for 30 min prior to receiving MDMA (0.0 or 10.0 mg/kg i.p.). Thereafter, locomotor (total, centre, and peripheral), and rearing activity were measured for 60 min. Two days following the last pre-treatment session (day 8), the locomotor activating response to MDMA (5.0 mg/kg, i.p.) was determined. During these tests, rats were placed into activity chambers and received MDMA after a 30 min period. Locomotor (total, centre, and peripheral) and rearing activity was recorded for 30 min prior to, and for 60 min following the administration of MDMA. This dosing regimen of MDMA was selected as we have previously demonstrated that it produces reliable sensitisation to the locomotor-activating effects of MDMA (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008). The MDMA challenge dose selected has been shown to reliably produce the expression of sensitisation, while being low enough to avoid ceiling effects (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008). These doses of eticlopride were used based on previous literature (Brennan et al., 2009; Bubar et al., 2004; Vezina, 1996; White, Joshi, Koeltzow, & Hu, 1998). This protocol is summarised in Table 2.

Table 2.
Summary of experiment 1 protocol

Days 1-5		Day 8	
Eticlopride	MDMA	Locomotor challenge	Sample size (*n)*
Saline	Saline	MDMA (5.0 mg/kg)	*n* = 10
Saline	10.0 mg/kg	MDMA (5.0 mg/kg)	*n* = 11
0.05 mg/kg	Saline	MDMA (5.0 mg/kg)	*n* = 8
0.05 mg/kg	10.0 mg/kg	MDMA (5.0 mg/kg)	*n* = 7
0.3 mg/kg	Saline	MDMA (5.0 mg/kg)	*n* = 8
0.3 mg/kg	10.0 mg/kg	MDMA (5.0 mg/kg)	*n* = 8

Experiment 2: procedure

Approximately one week following surgery, pre-treatment began, as above, with the exclusion of the 0.05 mg/kg eticlopride dose. Following two days of withdrawal, instead of receiving a locomotor challenge, these animals began self-administration testing (day 8). Daily 2 hr sessions were conducted, six days per week. Prior to, and immediately after each session, catheters were flushed with 0.2 ml of the penicillin-heparin solution. Every 7th day, catheter patency was confirmed by the immediate loss of the righting reflex following administration of sodium pentobarbital (22.5 mg/kg, i.v.). Because of the nature of the study, catheters were unable to be repaired or replaced without interrupting the acquisition process. Thus, rats that failed to retain patent catheters were omitted from any further testing or analysis. Each session commenced with an experimenter-administered infusion of MDMA (1.0 mg/kg) to clear the catheter of the penicillin-heparin solution. Thereafter, MDMA (1.0 mg/kg) infusions were delivered according to an FR-1 schedule of reinforcement. As in our previous studies (Schenk et al., 2012), acquisition of MDMA self-administration was defined as the self-administration of at least 90 MDMA (1.0 mg/kg) infusions within 25 test sessions.

For rats that met acquisition criteria, the infusion dose of MDMA was decreased to 0.5 mg/kg until a further 150 infusions had been self-administered. Rats that meet this second criterion remained in their home cages for two days of withdrawal before the locomotor activating effect of MDMA (5 mg/kg, i.p.) was measured. During these tests, rats were placed into activity chambers and received MDMA after a 30 min period. Locomotor activity was recorded for 60 min following the administration of MDMA. This protocol is summarised in table 3.

Table 3.
Summary of experiment 2 protocol

Days 1-5		Day 8+				
Eticlopride	MDMA	MDMA self-administration 90 infusions		MDMA self-administration 150 infusions	Locomotor challenge	Sample size (*n*)
Saline	Saline	1.0 mg/kg	→	0.5 mg/kg	→ MDMA 5mg/kg	*n* = 12
Saline	10.0 mg/kg	1.0 mg/kg		0.5 mg/kg	MDMA 5mg/kg	*n* = 12
0.3 mg/kg	Saline	1.0 mg/kg		0.5 mg/kg	MDMA 5mg/kg	*n* = 12
0.3 mg/kg	10.0 mg/kg	1.0 mg/kg		0.5 mg/kg	MDMA 5mg/kg	*n* = 12

Drugs

MDMA HCl (±3,4-methylenedioxymethamphetamine hydrochloride; ESR Porirua, New Zealand) was dissolved in sterile 0.9% saline and injected at a volume of 1 mg/ml, i.p. For i.v. self-administration infusions, MDMA was dissolved in 3 IU/ml heparinised 0.9% saline. S-(−)-Eticlopride hydrochloride (Sigma-Aldrich Castle Hill, Australia) was dissolved in sterile 0.9% saline solution and injected at a volume of 1 mg/ml, i.p. All drug weights refer to the salt.

Data analysis

Experiment 1. Individual two-way mixed measures analysis of variance (ANOVA) were conducted to analyse total, centre, and peripheral locomotor activity data during the five pre-treatment sessions as a function of pre-treatment. To investigate the relative change in centre and peripheral activity over the five pre-treatment sessions, these data were also calculated as a percentage change from baseline (group average from session 1) and analysed using a 2 (box zone: centre, periphery) × 5 (session: 1-5) repeated measures ANOVA. The locomotor challenge data were analysed using separate 3 (eticlopride dose: 0.0, 0.05, 0.3) × 2 (MDMA dose: 0.0, 10.0) ANOVAs on total, centre, and peripheral locomotor activity data. Due to technical difficulties, rearing data from experiment 1 were not available.

Experiment 2. Individual two-way mixed measures ANOVA's were conducted to analyse total, centre, peripheral and rearing activity data during the five pre-treatment sessions as a function of pre-treatment. To investigate the relative change in centre and peripheral activity over the five pre-treatment sessions, these data were also calculated as a percentage change from baseline (group average from session 1) and analysed using a 2 (box zone: centre, periphery) × 5 (session: 1-5) repeated measures ANOVA. Due to loss of catheter patency, only 6 - 9 rats per pre-treatment group finished the self-administration experiment. Therefore, only data from these rats were included in further analysis. For each rat that met acquisition criteria, the number of inactive and active lever responses were averaged over the first three days of self-administration and over the final three days prior to meeting criteria. A 2 (lever: inactive, active) × 2 (time: first 3 days, last 3 days) repeated measures ANOVA was conducted to test a preference for the active lever. The number of sessions to reach acquisition criteria was determined for each rat and the cumulative percentage of rats that met the criterion was determined as a function of test session for each pre-treatment group. Kaplan-Meier survival analyses (log-rank tests) were

used to compare the effect of pre-treatment on the cumulative percentage of rats that met the acquisition criterion for MDMA self-administration as a function of test session. Right-censoring was applied to the data for rats that did not meet the acquisition criterion within the 25 day cut-off. A 2 (self-administration experience: none, 165 mg/kg) × 2 (eticlopride dose: 0.0, 0.3) ANOVA was conducted to compare locomotor challenge data following self-administration with locomotor challenge data from experiment 1. Rats pre-treated with MDMA (0.0 mg/kg) were omitted from these analysis since too few rats met the second acquisition criteria.

For significant two-way interactions, simple main effect analyses were carried out to probe for differences using a Bonferroni corrected alpha level. Significant effects revealed by these tests were followed up with Bonferroni pairwise comparisons or Tukey post hoc tests. Degrees of freedom were adjusted (Greenhouse-Geisser) for tests of within-subjects effects when the assumption of sphericity had been violated, as assessed by Mauchly's test of sphericity. The level of significance for all tests was $p < .05$.

Results

Experiment 1: MDMA-induced behavioural sensitisation.

Development of sensitisation. Figure 1 shows the total (top), centre (centre), and peripheral (bottom) locomotor activity produced by the various pre-treatment conditions during the five pre-treatment sessions. The left column displays the effect of eticlopride (0.0, 0.05, 0.3 mg/kg) on saline-produced locomotor activity. The centre column displays the effect of MDMA (0.0 or 10.0 mg/kg) following a saline injection on locomotor activity. The right column displays the effect of eticlopride (0.0, 0.05, 0.3 mg/kg) on MDMA-produced locomotor activity.

To probe whether eticlopride (0.0, 0.05, 0.3 mg/kg) alone influenced basal (saline-produced) locomotor activity (figure 1 - left column), these data were subjected to separate 3 (eticlopride dose) × 5 (session) mixed measures ANOVAs on total, centre, and peripheral locomotor activity. The statistical values for these tests are displayed in appendix A: table A1. All three ANOVAs returned significant interactions. However, there were no significant simple main effects of eticlopride dose on any of the five sessions for total, centre, or peripheral locomotor activity indicating that eticlopride did not influence basal locomotor activity.

To examine the effect of repeated MDMA (0.0 or 10.0 mg/kg) exposure on locomotor activity (figure 1 - centre column), separate 2 (MDMA dose) × 5 (session)

mixed measures ANOVAs were conducted on total, centre, and peripheral locomotor activity. The statistical values for these tests are displayed in table A2. The ANOVAs on total and peripheral locomotor activity failed to reveal significant interactions or main effects of session, but produced significant main effects of MDMA dose indicating that MDMA 10.0 mg/kg increased total and peripheral locomotor activity. The ANOVA on centre locomotor activity returned a significant interaction. Simple main effect analyses revealed that MDMA (10.0 mg/kg) increased centre locomotor activity on all five sessions. There was also a significant simple main effect of session on MDMA (10.0 mg/kg); simple comparisons revealed that MDMA-produced centre locomotor activity was greater on sessions 3 and 5 compared to session 2.

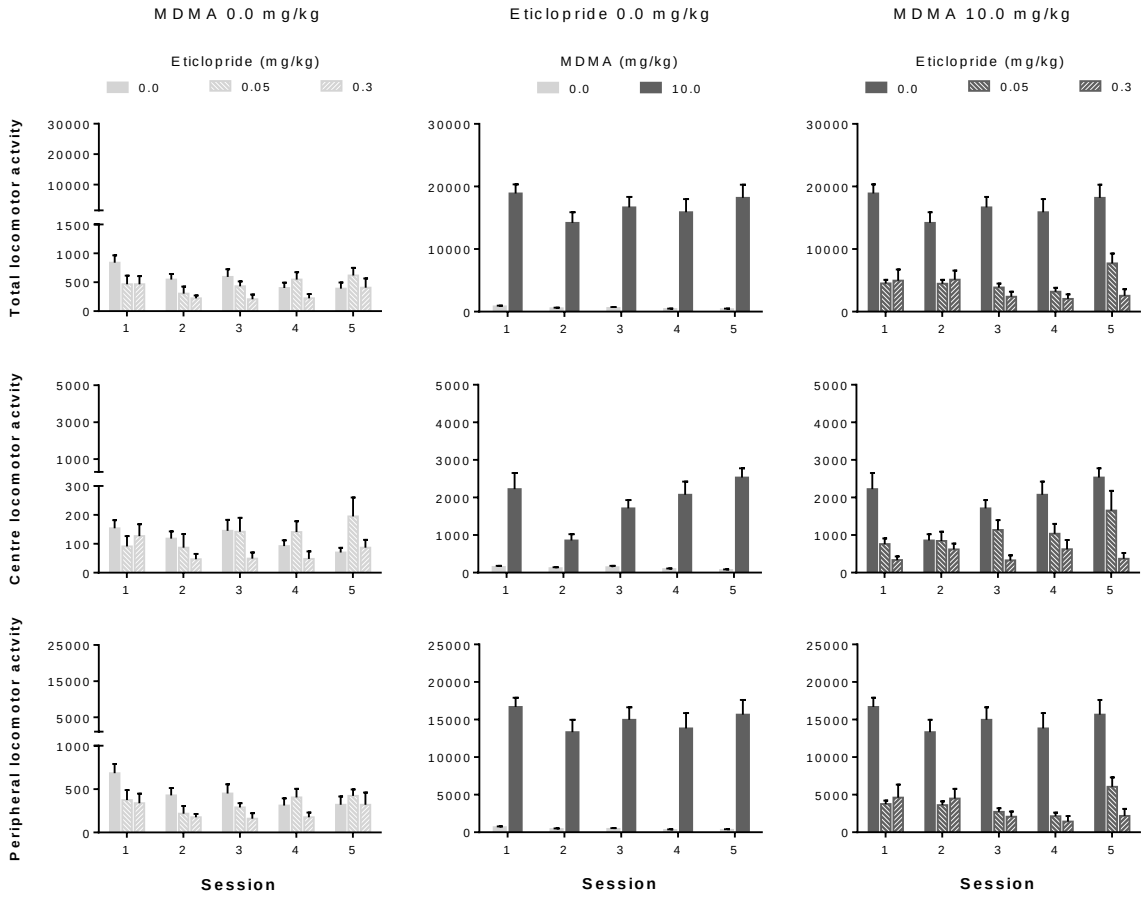

Figure 1. Average total (top), centre (centre), and peripheral (bottom) locomotor activity during the five days of pre-treatment for the various pre-treatment conditions in experiment 1. The left column displays the effect of eticlopride (0.0, 0.05, 0.3 mg/kg) on saline-produced locomotor activity. The centre column displays the effect of MDMA (0.0, 10.0 mg/kg) following a saline injection. The right column displays the effect of eticlopride (0.0, 0.05, 0.3 mg/kg) on MDMA-(10.0 mg/kg) produced locomotor activity. Error bars represent standard error of the mean.

To probe whether eticlopride (0.0, 0.05, 0.3 mg/kg) influenced MDMA-produced locomotor activity (figure 1 - right column), separate 3 (eticlopride dose) × 5 (session) mixed measures ANOVAs were conducted on total, centre, and peripheral locomotor activity. The statistical values for these tests are displayed in table A3. The ANOVAs on total and peripheral locomotor activity failed to reveal significant interactions but produced significant main effects of eticlopride dose. Tukey post hoc analyses revealed that eticlopride 0.05 mg/kg and 0.3 mg/kg attenuated MDMA-produced total and peripheral locomotor activity. The ANOVA on centre locomotor activity returned a significant interaction. There were significant simple main effects of eticlopride dose on all sessions except session 2. Tukey post hoc analyses revealed MDMA-produced locomotor activity was attenuated by eticlopride 0.05 mg/kg on session 1 and by eticlopride 0.3 mg/kg on sessions 1, 3, 4, and 5.

Centre versus peripheral activity. Figure 2 displays the percentage change in MDMA- (10.0 mg/kg) produced centre and peripheral locomotor activity relative to session one. A 2 (box zone) × 5 (session) repeated measures ANOVA produced a significant interaction (statistical values are displayed in table A4). Simple main effect analyses revealed that the percentage change in centre locomotor activity was lower than the percentage change in peripheral locomotor activity on session 2. There was also a simple main effect of session on the percentage change in centre locomotor activity; simple comparisons revealed that the percentage change in centre locomotor activity was lower on session 2 compared to sessions 3 and 5.

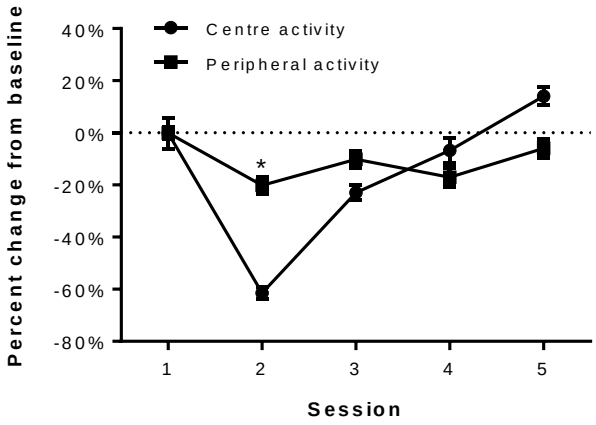

Figure 2. The average percentage change in centre and peripheral locomotor activity from baseline (session 1) during the five pre-treatment sessions for rats treated with MDMA (10.0 mg/kg) in experiment 1. Error bars represent standard error of the mean. * $p < .01$ between centre and periphery.

***Expression of locomotor sensitisation*.** Figure 3 shows the total, centre, and peripheral locomotor activity produced by MDMA (5 mg/kg) following two days of withdrawal from the various five-day pre-treatment regimens. Figure 3A displays total locomotor activity, which largely reflects peripheral activity. The statistical values for the following tests are displayed in table A5. A 3 (eticlopride dose) × 2 (MDMA dose) ANOVA on these data returned a significant interaction. Simple main effect analyses revealed that MDMA- (5 mg/kg) produced total locomotor activity was greater in rats pre-treated with MDMA (10.0mg/kg) indicating a sensitised locomotor response. There was also a significant simple main effect of eticlopride on MDMA- (10.0 mg/kg) produced sensitisation; simple comparisons revealed that co-administration of eticlopride 0.05 mg/kg and 0.3 mg/kg during pre-treatment blocked the sensitised locomotor response observed in MDMA pre-treated rats.

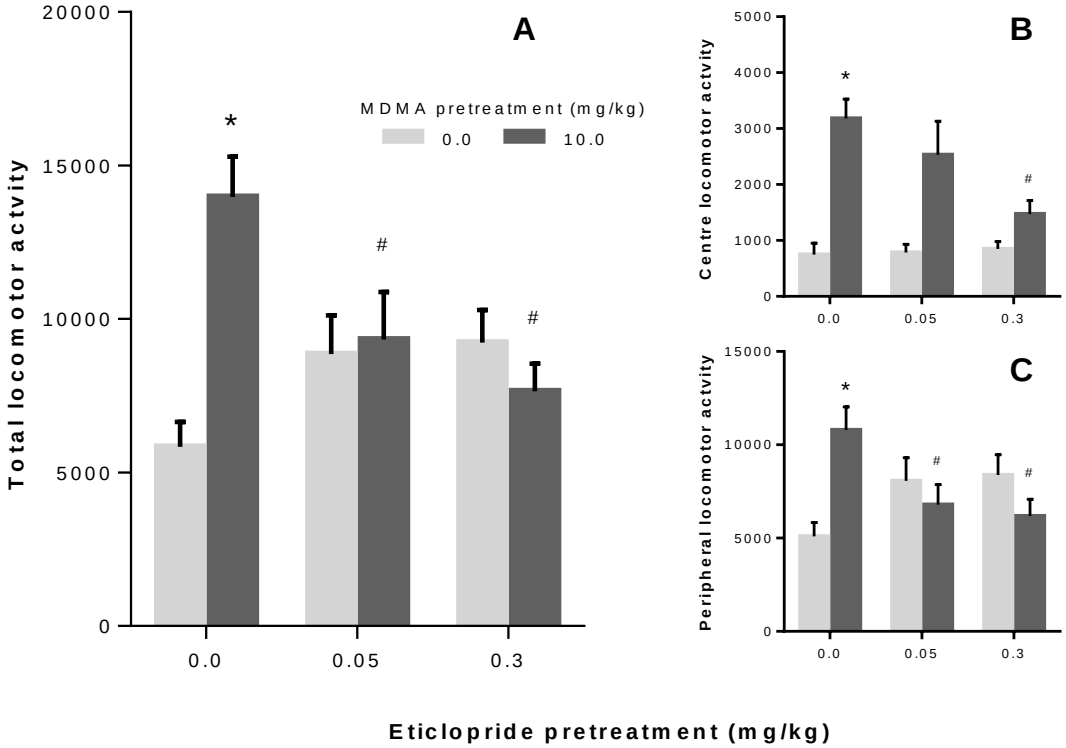

Figure 3. Average total (A), centre (B), and peripheral (C) locomotor activity produced by MDMA (5 mg/kg) following two days of withdrawal from pre-treatment with eticlopride (0.0, 0.05, 0.3 mg/kg) and MDMA (0.0, 10.0 mg/kg). Error bars represent standard error of the mean. * $p < .05$ compared to eticlopride (0.0 mg/kg) / MDMA (0.0 mg/kg) pre-treatment. $^{\#}$ $p < .05$ compared to eticlopride (0.0 mg/kg) / MDMA (10.0 mg/kg) pre-treatment.

Figure 3B and figure 3C displays the centre and peripheral locomotor activity, respectively. Separate 3 (eticlopride dose) × 2 (MDMA dose) ANOVAs on these data returned significant interactions. Simple main effect analyses revealed sensitised centre and peripheral locomotor responses for rats pre-treated with MDMA. There were also simple main effects of eticlopride on MDMA- (10.0 mg/kg) produced sensitisation of centre and peripheral locomotor activity; simple comparisons revealed that co-administration of both doses of eticlopride (0.05 and 0.3 mg/kg) during pre-treatment blocked the development of the sensitised peripheral response whereas only the high dose of eticlopride (0.3 mg/kg) blocked the sensitised centre response.

Figure 4 displays total locomotor activity in the 30 min prior to the administration of MDMA (5 mg/kg). A 3 (eticlopride dose) × 2 (MDMA dose) ANOVA failed to reveal a significant interaction, main effect of eticlopride dose, or main effect of MDMA dose, indicating that basal locomotor activity did not significantly differ as a function of pre-treatment.

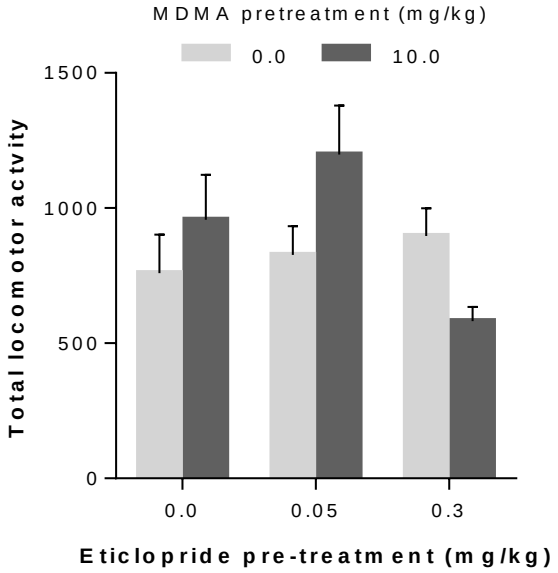

Figure 4. Average locomotor activity during the 30 min prior to the MDMA challenge as a function of pre-treatment with eticlopride (0.0, 0.05, 0.3 mg/kg) and MDMA (0.0, 10.0 mg/kg). Error bars represent standard error of the mean.

Experiment 2: Acquisition of MDMA self-administration

Development of locomotor sensitisation. Locomotor activity data during pre-treatment were largely similar between experiment one and two. Figure 5 shows the total (top), centre (centre), and peripheral (bottom) locomotor activity produced by the various pre-treatment conditions during the five pre-treatment sessions. The left column displays the effect of eticlopride (0.0 or 0.3 mg/kg) on saline-produced locomotor activity. The centre column displays the effect of MDMA (0.0 or 10.0 mg/kg) following a saline injection on locomotor activity. The right column displays the effect of eticlopride (0.0 or 0.3 mg/kg) on MDMA-produced locomotor activity.

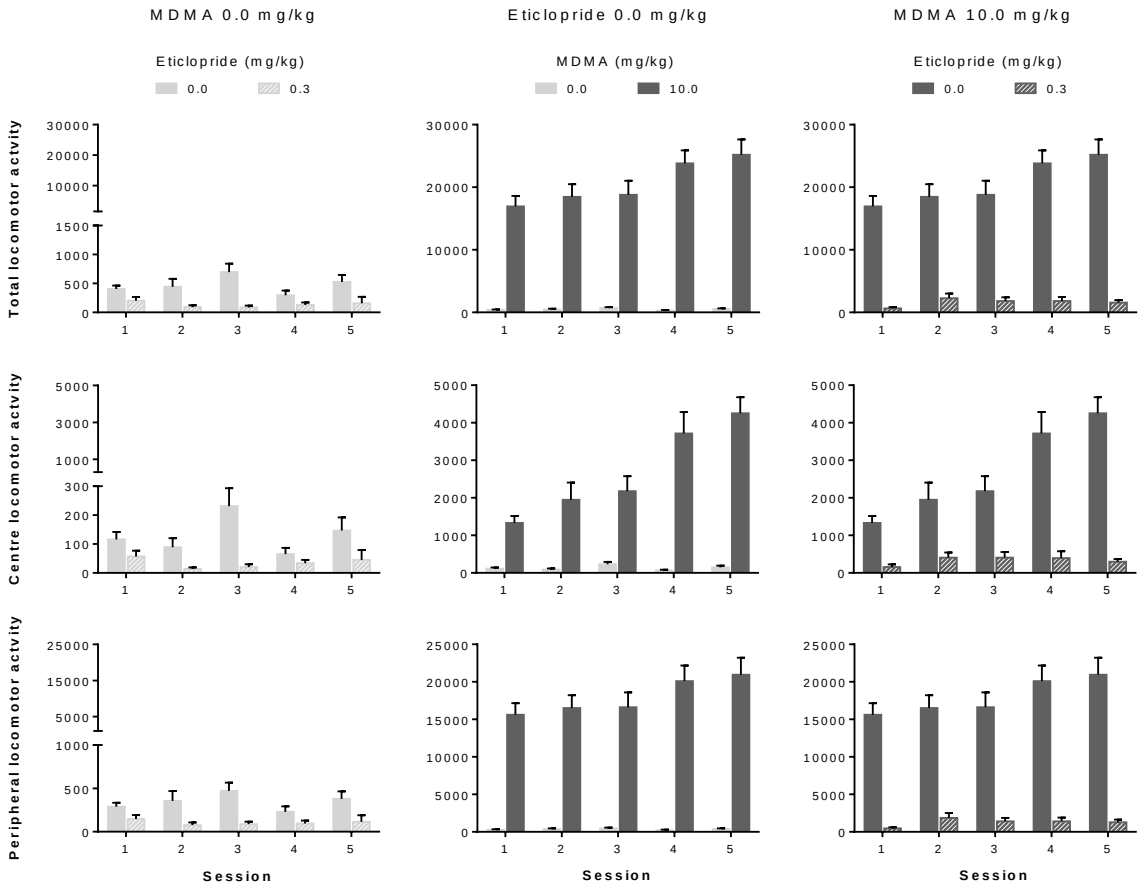

Figure 5. Average total (top), centre (centre), and peripheral (bottom) locomotor activity during the five days of pre-treatment for the various pre-treatment conditions in experiment 2. The left column displays the effect of eticlopride (0.0, 0.3 mg/kg) on saline produced locomotor activity. The centre column displays the effect of MDMA (0.0, 10.0 mg/kg) following a saline injection. The right column displays the effect of eticlopride (0.0, 0.3 mg/kg) on MDMA (10.0 mg/kg) produced locomotor activity. Error bars represent standard error of the mean.

To probe whether eticlopride (0.0 or 0.3 mg.kg) alone influenced basal (saline-produced) locomotor activity (figure 5 - left column), these data were subjected to separate 2 (eticlopride dose) × 5 (session) mixed measures ANOVAs on total, centre, and peripheral locomotor activity. The statistical values of these tests are displayed in appendix B: table B1. The ANOVAs on total and peripheral locomotor activity failed to reveal significant interactions but produced significant main effects of eticlopride dose indicating that eticlopride 0.3 mg/kg attenuated basal total and peripheral locomotor activity. The ANOVA on centre locomotor activity produced a significant interaction. Simple main effect analyses revealed that eticlopride 0.3 mg/kg attenuated basal centre locomotor activity on session 3.

To examine the effect of repeated MDMA (0.0 or 10.0 mg/kg) exposure on locomotor activity (figure 5 - centre column), separate 2 (MDMA dose) × 5 (session) mixed measures ANOVAs were conducted on total, centre, and peripheral locomotor activity. The statistical values of these tests are displayed in table B2. The ANOVAs on total and centre locomotor activity returned significant interactions. Simple main effects analyses revealed that MDMA 10.0 mg/kg increased total and centre locomotor activity on all five sessions. There were also significant simple main effects of session on MDMA (10.0 mg/kg); simple comparisons failed to find any differences between sessions for MDMA-produced total locomotor activity but revealed that MDMA-produced centre locomotor activity was greater on sessions 4 and 5 compared to session 1. The ANOVA on peripheral locomotor activity failed to reveal a significant interaction or main effect of session, but produced a significant main effect of MDMA dose indicating that MDMA 10 mg/kg increased peripheral locomotor activity.

To probe whether eticlopride (0.0 or 0.3 mg/kg) influenced MDMA-produced locomotor activity (figure 5 - right column), separate 2 (eticlopride dose) × 5 (session) mixed measures ANOVAs were conducted on total, centre, and peripheral locomotor activity. The statistical values of these tests are displayed in table B3. The ANOVAs on total and peripheral locomotor activity failed to reveal significant interactions but produced significant main effects of eticlopride dose indicating that eticlopride 0.3 mg/kg attenuated MDMA-produced total and peripheral locomotor activity. The ANOVA on centre locomotor activity returned a significant interaction. Simple main effect analyses revealed that eticlopride 0.3 mg/kg attenuated MDMA-produced centre locomotor activity on all five sessions.

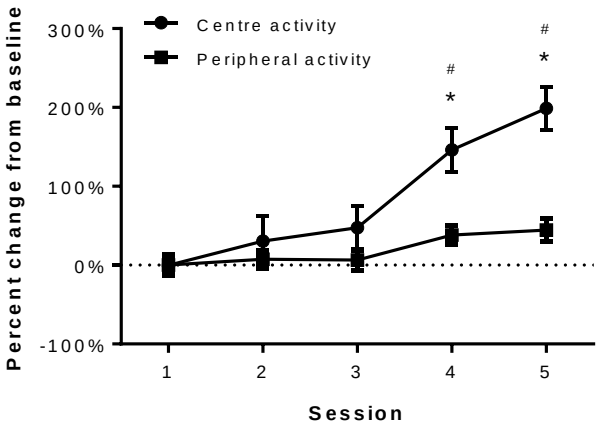

Figure 6. The average percentage change in centre and peripheral locomotor activity from baseline (session 1) during the five pre-treatment sessions for rats treated with MDMA (10.0 mg/kg) in experiment 2. Error bars represent standard error of the mean. * $p < .01$ between centre and periphery. $^{\#}$ $p < .025$ compared to session 1.

Centre versus peripheral locomotor activity. Figure 6 displays the percentage change in MDMA- (10.0 mg/kg) produced centre and peripheral locomotor activity relative to session one. A 2 (box zone) × 5 (session) repeated measures ANOVA produced a significant interaction (the statistical values are displayed in table B4). Simple main effect analyses revealed that the percentage change in centre locomotor activity was greater than the percentage change in peripheral locomotor activity on sessions 4 and 5. There were also significant simple main effects of session on the percentage change in centre and peripheral locomotor activity; simple comparisons failed to find any differences between sessions for peripheral locomotor activity, but revealed that the percentage change in centre locomotor activity was greater on session 4 and 5 compared to session 1.

Rearing activity. Figure 7 displays rearing activity produced by the various pre-treatment conditions during the five treatment sessions. The left panel displays the effect of eticlopride (0.0 or 0.3 mg/kg) on basal (saline-produced) rearing activity. A 2 (eticlopride dose) × 5 (session) mixed measures ANOVA failed to reveal a significant interaction, or main effect of eticlopride dose, indicating that basal rearing activity was not influenced by eticlopride (statistical values are displayed in table B5). The centre panel displays the effect of MDMA (0.0 or 10.0 mg/kg) following a saline injection on rearing activity. A 2 (MDMA dose) × 5 (session) mixed measures ANOVA produced a significant interaction (statistical values displayed in table B6). Simple main effect analyses revealed

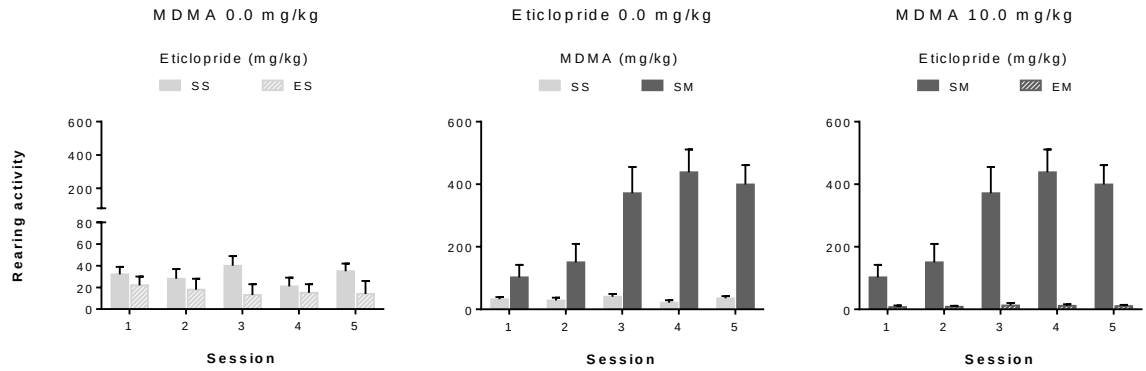

Figure 7. Average rearing activity during the five days of pre-treatment for the various pre-treatment conditions in experiment 2. The left panel displays the effect of eticlopride (0.0, 0.3 mg/kg) on saline produced rearing activity. The centre panel displays the effect of MDMA (0.0, 10.0 mg/kg) following a saline injection. The right panel displays the effect of eticlopride (0.0, 0.3 mg/kg) on MDMA (10.0 mg/kg) produced rearing activity. Error bars represent standard error of the mean.

that MDMA 10.0 mg/kg increased rearing activity on sessions 3, 4, and 5. There was also a significant simple main effect of session on MDMA 10.0 mg/kg; simple comparisons revealed that MDMA- (10.0 mg/kg) produced rearing was greater on sessions 3, 4, and 5, compared to session 1. The right panel displays the effect of eticlopride (0.0 or 0.3 mg/kg) on MDMA-produced rearing activity. A 2 (eticlopride dose) × 5 (session) mixed measures ANOVA produced a significant interaction (statistical values displayed in table B7). Simple main effect analyses revealed that eticlopride 0.3 mg/kg attenuated MDMA-produced rearing activity on sessions 3, 4, and 5.

Acquisition of self-administration. Figure 8 displays the average number of inactive and active lever responses over the first three days of self-administration and the final three days prior to meeting acquisition criteria (for the rats that did; $n = 26$). A 2 (lever) × 2 (time) repeated measures ANOVA on these data produced a significant interaction, $F(1, 25) = 70.85$, $p < .001$, $\eta_p^2 = .739$. Simple main effect analyses revealed a significant preference for the active lever on the last three days of self-administration, $F(1, 25) = 63.09$, $p < .001$, $\eta_p^2 = .716$, but not on the first three days ($p = .189$; level of significance accepted at $p < .025$). Simple main effects also revealed a significant increase in the number of active lever responses, $F(1, 25) = 103.74$, $p < .001$, $\eta_p^2 = .806$, but found no change in the number of left lever responses ($p = .849$; level of significance accepted at $p < .025$).

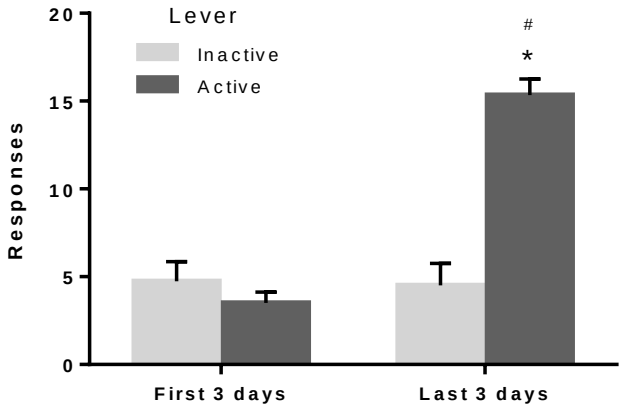

Figure 8. Average number of responses made on the inactive and active levers over the first three days of self-administration and the final three days prior to meeting acquisition criteria for the rats that acquired (n = 26). Error bars represent standard error of the mean. * $p < .025$ compared to inactive lever on the last three days. # $p < .025$ compared to active lever on the first three days.

Figure 9 displays the cumulative percentage of rats that met the acquisition criteria for MDMA self-administration for the various pre-treatment groups. The top panel shows that 44.44% of saline pre-treated control animals met the acquisition criterion compared to 100% of rats pre-treated with MDMA. A significant Log-rank, Kaplan-Meier analysis indicated that the likelihood to meet acquisition criteria was greater for subjects pre-treated with MDMA, $\chi^2(1) = 10.29$, $p < .001$.

The centre panel shows that 77.8% of rats pre-treated with eticlopride + MDMA met acquisition criteria compared to 100% of MDMA only pre-treated rats. A Log-rank, Kaplan-Meier survival analysis failed to reveal a difference between these two pre-treatment groups indicating that co-administration of eticlopride failed to block the facilitation of MDMA self-administration observed in MDMA pre-treated rats ($p = .628$).

The bottom panel shows the 100% of rats pre-treated with eticlopride alone met acquisition criteria compared to 44.44% of saline pre-treated controls. A significant Log-rank, Kaplan-Meier survival analysis indicated that the likelihood to meet acquisition criteria was greater for subjects pre-treated with eticlopride alone, $\chi^2(1) = 8.66$, $p = .003$.

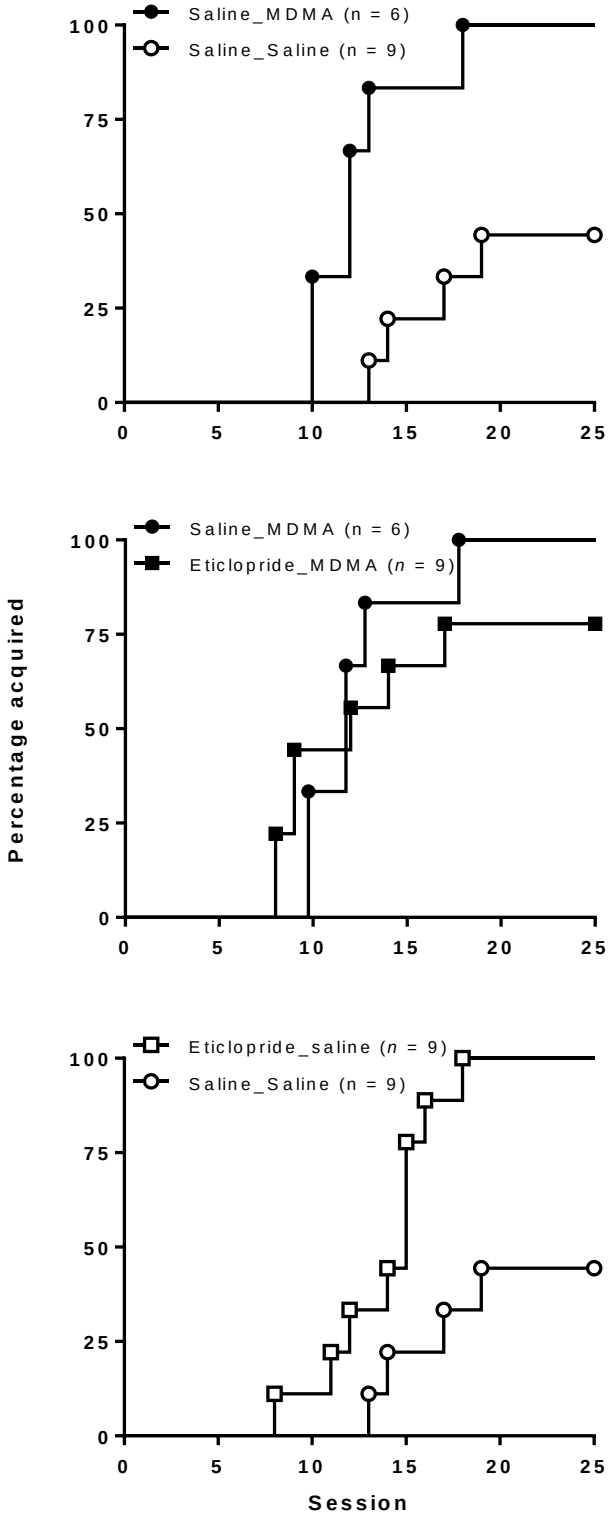

Figure 9. Cumulative percentage of rats that met acquisition criteria for MDMA self-administration over the 25 daily sessions following two days of withdrawal from the various pre-treatment conditions. The first listing in each legend indicates the eticlopride pre-treatment (saline, 0.3 mg/kg) and the second listing indicates the MDMA pre-treatment (saline, 10.0 mg/kg). Sample sizes are also indicated in each legend.

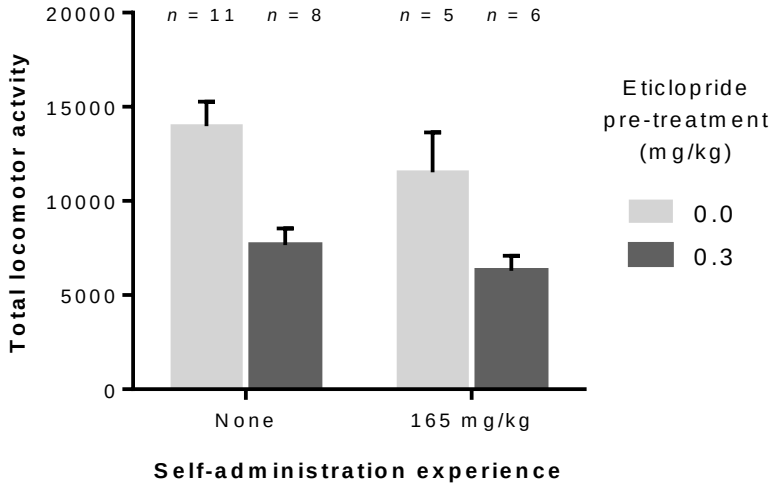

Figure 10. Average total locomotor activity produced by MDMA (5 mg/kg) for rats pre-treated with eticlopride (0.0, 0.3 mg/kg) and MDMA (10.0 mg/kg) with or without self-administration experience. Error bars represent standard error of the mean.

Expression of locomotor sensitisation. Figure 10 displays the effect of eticlopride pre-treatment and self-administration experience on total locomotor activity produced by MDMA (5 mg/kg) following two days of withdrawal for rats pre-treated with MDMA 10.0 mg/kg. A 2 (eticlopride dose) × 2 (self-administration experience) ANOVA failed to reveal a significant interaction (p = .694) or a main effect of self-administration experience (p = .180) indicating that MDMA self-administration experience did not influence MDMA-produced locomotor activity. A main effect of eticlopride dose, $F(1, 26) = 17.43$, $p < .001$, $\eta_p^2 = .401$, indicated that co-administration of eticlopride 0.3 mg/kg during pre-treatment attenuated the subsequent locomotor activating effects of MDMA regardless of self-administration experience.

Discussion

The aims of the present research were twofold. The first experiment investigated the role of D_2 receptors in the development of sensitised MDMA-produced horizontal and vertical (rearing) locomotor activity following repeated intermittent exposure. The second experiment determined whether repeated intermittent exposure to MDMA would also sensitise to the reinforcing effects of MDMA, as measured by the acquisition of self-administration, and determined the role of D_2 receptor mechanisms.

Experiment 1: MDMA-induced behavioural sensitisation

It is generally accepted that sensitised central DAergic mechanisms play an important role in the development and expression of behavioural sensitisation (Kalivas & Stewart, 1991; Pierce & Kalivas, 1997; Vanderschuren & Kalivas, 2000). This appears equally true for MDMA since repeated MDMA exposure produced behavioural sensitisation that was accompanied by sensitised DAergic responses in the NAcc (Kalivas et al., 1998) and changes in accumbal c-Fos expression (Colussi-Mas & Schenk, 2008). Moreover, repeated MDMA exposure resulted in cross-sensitisation to other, more potent, DAergic drugs including amphetamine and cocaine (Bradbury et al., 2012; Kalivas et al., 1998). Both D_1- and D_2-like receptor mechanisms have been implicated since cross-sensitisation to D_1 and D_2 agonists was also produced (Bradbury et al., 2012). Little is known about the involvement of these receptors in the development of MDMA sensitisation, however. Because the D_1 antagonist, SCH-23390, failed to block the development of MDMA sensitisation (Ramos et al., 2004), the purpose of the first experiment was to determine the role of D_2 receptors in the development of MDMA sensitisation.

Repeated intermittent exposure to MDMA sensitised rats to the subsequent locomotor activating effects of MDMA, a finding that we, and several other researchers have previously demonstrated (Ball, Budreau, & Rebec, 2006; Bradbury et al., 2012; Colussi-Mas & Schenk, 2008; Kalivas et al., 1998; Ramos et al., 2004; Spanos & Yamamoto, 1989). As was hypothesised, the development of this sensitised response was prevented by the co-administration of the D_2 antagonist, eticlopride, during MDMA pre-treatment. This suggests that activation of D_2 receptors is critical to the development of MDMA sensitisation. D_2 receptor antagonists have also been found to prevent the development of methamphetamine sensitisation (Hamamura et al., 1991; Kuribara & Uchihashi, 1993, 1994; Kuribara, 1995, 1996) but have yielded mixed result regarding amphetamine and cocaine sensitisation (see Vanderschuren & Kalivas, 2000).

Because D_2 receptors function as postsynaptic heteroreceptors and as presynaptic autoreceptors, the nature of their involvement in MDMA sensitisation is not entirely straightforward. Compared to postsynaptic D_2 receptors, D_2 autoreceptors have greater affinity for dopamine and D_2 ligands but are less abundant (Castro & Strange, 1993; Malmberg, Jackson, Eriksson, & Mohell, 1993; Missale et al., 1998). As such, the same D_2 ligand can produce a biphasic effect, preferentially affecting D_2 autoreceptors when

administered at lower concentrations and acting on the more abundant postsynaptic receptors when administered at higher concentrations (Beaulieu & Gainetdinov, 2011). For example, a low dose of the $D_{2/3}$ agonist, quinpirole (0.03 mg/kg), decreased locomotor activity whereas higher doses (0.5 – 8.0 mg/kg) increased locomotor activity (Eilam & Szechtman, 1989). In the present study, relatively high doses of eticlopride were used that completely blocked MDMA-produced locomotor activity. This effect could only be due to antagonism of postsynaptic D_2 receptors since selective antagonism of D_2 autoreceptors would have been expected to produce the opposite effect (Bello et al., 2011; Cabib, Castellano, Cestari, Filibeck, & Puglisi-Allegra, 1991; Eilam & Szechtman, 1989).

We have previously shown that repeated MDMA exposure also sensitised rats to the behavioural effects of relatively high doses of quinpirole (Bradbury et al., 2012), which suggests that that repeated MDMA exposure might lead to a sensitisation of postsynaptic D_2 receptor mechanisms. Given that eticlopride prevented the development of MDMA sensitisation (present findings), this neuroadaptation may be a mechanism underlying the development and expression of MDMA sensitisation. Several studies have found evidence for sensitised postsynaptic D_2 receptor mechanisms following repeated exposure to other drugs of abuse (De Vries, Schoffelmeer, Binnekade, & Vanderschuren, 1999; Ujike, Akiyama, & Otsuki, 1990; Vanderschuren, Schoffelmeer, Mulder, & De Vries, 1999). For example, rats exposed to a sensitising regimen of amphetamine were also sensitised to the behavioural effects of quinpirole and displayed an increased number of high affinity postsynaptic D_2 binding sites four weeks later (Seeman, McCormick, & Kapur, 2007). Future research could determine whether a sensitising regimen of MDMA exposure similarly leads to an increase in postsynaptic D_2 receptor binding sites and correlate this with sensitised behavioural responses.

To ensure that the present findings were not an artefact of differences in basal locomotor activity between the various pre-treatment groups, locomotor activity was measured during the initial 30 min prior to the MDMA challenge on day 8. There were no significant differences between pre-treatment groups indicating this was not a contributing factor. The possibility of a conditioned locomotor response to the i.p. injection, while unlikely, cannot be discounted, however, because the locomotor response to a saline injection was not measured. Although previous studies using the same pre-treatment regimen and testing methods failed to find a difference in saline-produced locomotor

activity between MDMA and saline pre-treated rats (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008).

Centre versus peripheral activity. The pattern of hyperactivity produced by MDMA differs from that produced by other psychostimulants in that it is typically restricted to the periphery of a closed chamber (Bradbury et al., 2012; Gold et al., 1988; Ludwig et al., 2008; McCreary et al., 1999; Palenicek et al., 2005). In order to gain more insight into the effects of repeated MDMA exposure, the present study also measured centre and peripheral locomotor activity. Acute MDMA administration produced far greater increases (6 – 10 fold) in peripheral activity compared to centre activity. As has been previously documented (Bradbury et al., 2012; Colussi-Mas & Schenk, 2008; Ludwig et al., 2008; McCreary et al., 1999), this profile of hyperactivity changed with repeated exposure. Total locomotor activity increased, but the relative increase in centre activity (314%) was greater than the relative increase in peripheral activity (168%). This cannot be due to a ceiling effect whereby peripheral activity simply cannot increase any further since peripheral activity produced by the MDMA (5 mg/kg) challenge was, at most, ~50% of that produced by the higher dose of MDMA (10 mg/kg) used during pre-treatment. Rather, it has been suggested that this effect reflects sensitisation of the DAergic effects of MDMA, as the pattern of hyperactivity begins to more closely resemble that produced by amphetamine (Bradbury et al., 2012).

The extent to which sensitised D_2 receptor mechanisms contribute to this effect is unclear. In the present study, although the higher dose of eticlopride (0.3 mg/kg) blocked the sensitisation of both centre and peripheral activity, the lower dose (0.05 mg/kg) failed to block the sensitisation of centre activity but still completely blocked the sensitisation of peripheral activity. Further, eticlopride (0.05 mg/kg) only significantly attenuated MDMA-produced centre activity during the first session of pre-treatment but consistently blocked MDMA-produced peripheral activity. It should be noted, though, that a floor effect may have occluded a significant attenuation of centre activity. Nevertheless, these findings allude to previous studies that have suggested D_2 receptors play a more prominent role in peripheral locomotor activity (Eilam, Clements, & Szechtman, 1991; Eilam, Golani, & Szechtman, 1989; Risbrough et al., 2006). Much like MDMA, quinpirole-produced hyperactivity was primarily restricted to the periphery of the activity chamber (Eilam et al., 1991, 1989). Further, a genetic deletion of D_2, but not D_1 or D_3 receptors, specifically decreased the amount of peripheral activity produced by MDMA (Risbrough et al., 2006).

Based on these findings, sensitisation of D_2 receptor mechanisms might explain the sensitisation of MDMA-produced peripheral activity but cannot explain the disproportionate sensitisation of centre activity.

One potential explanation is that repeated MDMA exposure also sensitises D_1 receptor mechanisms. Much like amphetamine, D_1 receptor agonists typically produce locomotor activity that is more generalised over the entire activity chamber (Eilam et al., 1991; Meyer, Van Hartesveldt, & Potter, 1993; Salmi & Ahlenius, 2000). Administration of the D_1 agonist, SKF-38393, dose-dependently increased the proportion of centre activity produced by quinpirole (Eilam et al., 1991), a change in the pattern of hyperactivity similar to that which occurs with repeated MDMA exposure. Thus, the disproportionate sensitisation of centre activity following repeated MDMA exposure might reflect sensitisation of D_1 receptor mechanisms. Although SCH-23390 did not block the development of MDMA locomotor sensitisation, centre and peripheral activity was not specifically measured (Ramos et al., 2004). Given that centre activity represents a small proportion of total locomotor activity produced by MDMA, even when sensitised, if SCH-23390 did block the development of centre activity sensitisation in this study it might not have significantly influenced total locomotor activity. To address this possibility, future research could investigate the effect of D_1 antagonists on the development of sensitisation to MDMA-produced centre activity.

Avoidance of the centre of a closed chamber has often been used as an index of anxiety (Crawley, 1985; Ennaceur, Michalikova, & Chazot, 2006; File, 2001). Thus, an increase in centre activity as a function of repeated MDMA exposure might alternatively reflect tolerance to the anxiogenic effects of MDMA. In support of this idea, more time was spent in the open arms of an elevated plus maze (Bull, Hutson, & Fone, 2004) and the latency to emerge from a hide box into an open field was decreased (Jones, Brennan, Colussi-Mas, & Schenk, 2010) following repeated MDMA exposure. These effects were attributed to 5-HTergic mechanisms since the dosing regimens used in these studies produced 5-HT depletion. The dosing regimen used in the present study, however, consisted of much lower doses of MDMA that did not produce 5-HT depletion (Bradbury et al., 2012). Changes in post-synaptic 5-HT receptor mechanisms or stimulated 5-HT release remain as possibilities, though, and could be measured following a similar regimen of repeated MDMA exposure in future research.

MDMA-produced locomotor activity data (total, centre and peripheral) during the five-days of pre-treatment were slightly different between experiment one and experiment two. Locomotor activity on day one, experiment one, was particularly high and therefore no changes in MDMA-produced locomotor activity were apparent over the five days of pre-treatment. In experiment two, however, locomotor activity on day one was relatively low and a gradual increase in MDMA-produced locomotor activity was observed during the five-day pre-treatment period, indicative of sensitisation. These inconsistencies might reflect differences in the handling of the rats between the two experiments (Gentsch, Lichtsteiner, Frischknecht, Feer, & Siegfried, 1988; Harkin, 2000; Pritchard, Van Kempen, & Zimmerberg, 2013). In experiment two, rats were handled daily prior to pre-treatment and had experience with injections due to the surgical procedure and post-operative care required for catheter implantation. In contrast, rats in experiment one were completely naive, with no handling or experience with injections. In order to determine whether this was the basis for the differences between experiments, additional studies could be conducted with comparable handling between groups.

Rearing activity. Acute MDMA administration typically supresses rearing activity (Callaway et al., 1990; Fone et al., 2002; Kehne et al., 1996; Ludwig et al., 2008; Sadananda et al., 2012; M. R. Thompson et al., 2007). In experiment two of the present research, acute MDMA (10 mg/kg) administration did not significantly influence total rearing activity; however, time course analysis revealed that MDMA significantly increased rearing activity during the final 20 min of the session (data not shown). Consistent with this finding, Gold and colleagues found that although MDMA initially supressed rearing, the highest dose of MDMA (10 mg/kg) increased rearing 90 min after administration (Gold et al., 1988).

During the five-day pre-treatment regimen, MDMA-produced rearing activity dramatically increased, indicative of sensitisation. This is consistent with findings from previous studies that have also found increased rearing activity following repeated MDMA exposure (Ludwig et al., 2008; Schenk & Bradbury, 2015). Evidence suggests that increased DAergic activity underlies rearing activity (Bubar et al., 2004; Hoffman & Beninger, 1985; Kalivas et al., 1984; Molloy & Waddington, 1985; Vazquez-DeRose et al., 2013). The increase in MDMA-produced rearing as a function of repeated exposure might, therefore, reflect the sensitisation of DAergic mechanisms. In support of this idea, acute administration of S(+)-MDMA, the more potent DA releasing isomer, typically

increases rearing activity whereas racemic ±MDMA, as mentioned previously, typically does not (Bubar et al., 2004; Callaway et al., 1990; Herin et al., 2005; Kehne et al., 1996; McCreary et al., 1999). Unfortunately, because rearing activity data were not available from experiment one, there was no specific test for the expression of rearing sensitisation. Therefore, the involvement of D_2 receptors in the development of this sensitised response was not determined. Rearing activity produced by acute MDMA administration was completely blocked by eticlopride, however, which is consistent with previous findings (Bubar et al., 2004).

The increase in rearing activity as a function of repeated MDMA exposure might alternatively reflect a decrease in behavioural competition between rearing activity and 5-HT syndrome behaviours. In rats, acute MDMA administration produces components of the 5-HT syndrome including flat body posture, splayed hind limbs, forepaw treading, and head weaving (Spanos & Yamamoto, 1989). These behaviours, particularly flat body posture, are incompatible with rearing activity. Indeed, MDMA-produced flat body posture was inversely related to rearing activity; acute S(+)-MDMA administration increased flat body posture primarily during the beginning of the test session and increased rearing during the end of the session (Bubar et al., 2004). Tolerance to 5-HT syndrome behaviours occurs rapidly and has been reported following repeated MDMA exposure under conditions that produced decreases in tissue levels of 5-HT (Baumann, Clark, Franken, et al., 2008; Shankaran & Gudelsky, 1999). As mentioned previously, the dosing regimen used in the present study did not produce 5-HT depletion (Bradbury et al., 2012), although decreases in stimulated 5-HT release or other 5-HTergic mechanisms may contribute to the tolerance of these behaviours. If so, an inverse relationship between MDMA produced 5-HT syndrome behaviours and rearing activity would be expected during a regimen of repeated MDMA exposure.

Experiment 2: Acquisition of MDMA self-administration

It has been suggested that DAergic neuroadaptations underlying behavioural sensitisation contributes to the formation of excessive drug-taking and drug-seeking behaviour (Robinson & Berridge, 1993). Support for this theory comes from several studies that have demonstrated that repeated exposure to drugs of abuse, under conditions that produced behavioural and DAergic sensitisation, facilitated the subsequent acquisition of self-administration and enhanced responding on progressive ratio schedules (for a review see Vezina, 2004). To the best of our knowledge, a similar experiment has not been

conducted using MDMA. We therefore determined the effect of a sensitising regimen of MDMA exposure on the subsequent acquisition of self-administration.

Consistent with what has been found with other drugs of abuse (see Vezina, 2004), repeated exposure to MDMA under conditions that produced behavioural sensitisation also produced sensitisation to the reinforcing effects of MDMA, as evidenced by a facilitated acquisition of self-administration. As expected, rats pre-treated with MDMA were more likely to meet acquisition criteria compared to saline pre-treated controls, which displayed similar acquisition rates to what we have previously found using naive subjects (Schenk et al., 2012).

Because sensitising regimens of MDMA exposure have been shown to enhance MDMA-produced NAcc DA release (Kalivas et al., 1998), and the reinforcing effects of MDMA have been attributed to DAergic mechanisms (Brennan et al., 2009; Daniela et al., 2004), sensitised central DAergic mechanisms may underlie the facilitated acquisition of self-administration observed in the present study. In support of this idea, naive rats that met acquisition criteria for MDMA self-administration displayed enhanced MDMA-produced striatal DA release (Colussi-Mas et al., 2010). Further, repeated MDMA exposure also facilitated the acquisition of cocaine self-administration (Fletcher et al., 2001), an effect that was attributed to sensitised central DAergic mechanisms induced by repeated MDMA exposure (Fletcher et al., 2001; Morgan et al., 1997). If enhanced MDMA-produced DA release underlies sensitisation to the reinforcing effects of MDMA, future research could measure MDMA-produced synaptic DA using *in vivo* microdialysis following the same regimen of repeated MDMA exposure and relate it to the subsequent acquisition of self-administration.

Eticlopride + MDMA pre-treatment. To determine the role of D_2 receptors, the effect of eticlopride pre-treatment in combination with MDMA on sensitisation to the reinforcing effects of MDMA was also determined. Procedures that prevent the development of behavioural and DAegric sensitisation have been shown to also prevent the subsequent facilitation of drug taking (Vezina, 2004). Therefore, since eticlopride blocked the development of MDMA sensitisation (experiment 1), it was hypothesised that eticlopride would also block the facilitated acquisition of MDMA self-administration observed in MDMA pre-treated rats. Although a lesser percentage of rats met acquisition criteria, the likelihood that a subject would meet acquisition criteria by day 25 was not significantly decreased by eticlopride + MDMA pre-treatment. These findings suggest that

while D_2 receptor mechanisms may play some role, other mechanisms contributed to the development of sensitisation to the reinforcing effects of MDMA.

One such mechanism might involve changes in 5-HT neurotransmission as a result of repeated MDMA exposure. Increased 5-HT is generally inhibitory the reinforcing effects of drugs abuse (e.g. McGregor et al., 1993; Roberts et al., 1999; Wee & Woolverton, 2006; Wee et al., 2005). This is particularly evident for MDMA; the acquisition of MDMA self-administration was greatly facilitated by 5-7 DHT lesions or a genetic mutation of the 5-HT transporter (Bradbury et al., 2013; Oakly et al., 2013). Further, MDMA-produced increases in NAcc 5-HT were negatively correlated with the propensity to self-administer MDMA (Bradbury et al., 2013). Tolerance to the 5-HTergic effects of MDMA, therefore, would be expected to facilitate the acquisition of self-administration. As previously mentioned, repeated exposure to high doses of MDMA produces deficits in 5-HTergic neurotransmission (see Baumann et al., 2007; Green et al., 2003; Ricaurte et al., 2000). Even though the dosing regimen used in the present study did not produce 5-HT depletion (Bradbury et al., 2012), changes in other indices of 5-HTergic neurotransmission following this particular dosing regimen have not been determined and might be a contributing factor. A decrease in stimulated 5-HT release, for example, has been demonstrated following repeated self-administered MDMA (Reveron et al., 2010) and would be expected to facilitate the acquisition of MDMA self-administration. Changes in postsynaptic 5-HT receptor mechanisms may also have been a contributing factor since a downregulation of 5-HT_{1a} receptors induced by pre-treatment with the $5\text{-HT}_{1a/1b}$ agonist, RU-24969, facilitated the acquisition of self-administration (Aronsen, Bukholt, & Schenk, 2016).

Therefore, as we have previously suggested (Schenk, 2011), both the sensitisation of DAergic mechanisms (including D_2 receptor mechanisms) and tolerance to the 5-HT releasing effects of MDMA might be contributing factors to the acquisition of reliable MDMA self-administration. Because we cannot determine that 5-HTergic neuroadaptations did not occur in the present study, the relative contribution of DAergic sensitisation and 5-HTergic tolerance remains to be elucidated. Future research could measure changes 5-HT receptor mechanisms or stimulated 5-HT release following a similar sensitising regimen of MDMA exposure. Alternatively, the effect of a sensitising regimen of more selective DAergic agonists, such as amphetamine or apomorphine, on the subsequent acquisition of MDMA self-administration could be determined.

Eticlopride pre-treatment. Interestingly, control rats pre-treated with eticlopride alone were also sensitised to the reinforcing effects of MDMA; 100% of these rats met acquisition criteria suggesting that D_2 receptor mechanisms do indeed influence the acquisition of MDMA self-administration. Several studies have found that repeated administration of D_2 antagonists results in an upregulation of these receptors (Braun, Laruelle, & Mouradian, 1997; Muller & Seeman, 1977; Tegner, 1977). For example, four days after receiving 21 days of daily eticlopride treatment (0.5 mg/kg), rats displayed an increased density of D_2 binding sites (LaHoste & Marshall, 1991). Thus, in the present study, repeated eticlopride treatment may have induced a homeostatic upregulation of post-synaptic D_2 receptors that facilitated the acquisition of MDMA self-administration.

If such an upregulation of postsynaptic D_2 receptors was evident two days following eticlopride pre-treatment, then a sensitised locomotor response to MDMA would also have been expected in experiment 1. Indeed, a post hoc one-way ANOVA revealed that eticlopride pre-treatment resulted in small increases in MDMA-produced locomotor activity that were approaching significance (p = .051; figure 3). Interestingly, these increases were only evident for peripheral locomotor activity, supporting previous suggestions that D_2 receptors play a more prominent role in peripheral activity (Eilam et al., 1991, 1989; Risbrough et al., 2006). Similar findings have been found by previous studies. For example, subchronic blockade of D_2 receptors in the VTA sensitised the locomotor activating effects of amphetamine (Tanabe, Suto, Creekmore, Steinmiller, & Vezina, 2004).

In another study, intermediate doses of the D_2 antagonist, sulpiride, attenuated-whereas high doses potentiated the development of methamphetamine sensitisation (Kuribara, 1996). Because of the longer half-life of sulpiride, the authors suggested that blockade of D_2 receptors by the high dose of sulpiride persisted long after the effects of methamphetamine had worn off, which resulted in the upregulation of D2 receptors. In the present study, the opposite may have occurred for rats pre-treated with eticlopride + MDMA. Because the half-life of MDMA is much longer than eticlopride (R. L. Fitzgerald, Blanke, & Poklis, 1990; Norman, Tabet, Norman, & Tsibulsky, 2011), and because eticlopride was administered 30 min prior to MDMA, D_2 receptor activation by MDMA may have persisted after the effects of eticlopride had worn off. Although this activation was evidently not enough to induce sensitisation, this may have prevented the upregulation of D_2 receptors for rats that received eticlopride + MDMA. This would explain why an

additive effect of eticlopride + MDMA treatment was not observed in experiment one or two.

Behavioural sensitisation. In order to examine the effect of self-administration experience on MDMA-induced sensitisation, the locomotor activating effect of MDMA was tested after a total of 165 mg/kg MDMA had been self-administered and compared to rats with no self-administration experience (experiment 1). Because too few saline pre-treated controls met this second self-administration criterion, these comparisons were only made for rats pre-treated with MDMA (10 mg/kg) alone or in combination with eticlopride.

It might have been expected that the additional MDMA exposure during self-administration would have potentiated the sensitised response produced by MDMA pre-treatment. Whereas for the rats pre-treated with eticlopride + MDMA (which were not sensitised to MDMA), it might have been expected that the additional exposure to MDMA without eticlopride treatment would have resulted in the development of a sensitised response. Locomotor responses to MDMA (5 mg/kg) did not differ between rats with or without self-administration experience, however, regardless of pre-treatment. Previous studies have shown that repeated MDMA exposure in a different environmental context fails to induce MDMA sensitisation (Ball et al., 2006; Ball, Klein, Plocinski, & Slack, 2011). Because the additional exposure to MDMA was received in the context of self-administration, this may not have influenced MDMA-produced locomotor activity in the locomotor testing chambers.

Conclusions

In experiment one, the role of D_2 receptors in the development of sensitised MDMA-produced horizontal and vertical (rearing) locomotor activity following repeated intermittent exposure was determined. Repeated intermittent MDMA exposure sensitised rats to the locomotor activating effects of MDMA. Sensitisation of locomotor activity was proportionately greater in the centre than in the periphery of the activity chamber. Rearing activity also appeared to become sensitised with repeated MDMA exposure. The development of these sensitised behavioural responses was prevented by the co-administration of eticlopride during MDMA pre-treatment indicating a critical role of D_2 receptors. It is suggested that repeated MDMA exposure results in the sensitisation of postsynaptic D_2 receptors, which enhanced the locomotor activating effects of MDMA.

In experiment two, the effect of a sensitising regimen of MDMA exposure on the subsequent acquisition of MDMA self-administration was determined. As expected, pre-treatment with MDMA sensitised the reinforcing effects of MDMA, evidenced by a facilitated acquisition of self-administration. Because the DAergic mechanisms underlying sensitisation to the locomotor activating and reinforcing effects of drugs of abuse are thought to be similar (Vezina, 2004), the contribution of D_2 receptor mechanisms was also investigated. Eticlopride failed to completely block the facilitated acquisition of MDMA self-administration observed in MDMA pre-treated rats. This suggests that while D_2 receptor mechanisms may play some role, other mechanisms, such as tolerance to the 5-HT release effects of MDMA, may contribute to the development of sensitisation to the reinforcing effects of MDMA. Finally, MDMA self-administration did not influence MDMA-produced locomotor activity, regardless of pre-treatment, emphasising the importance of environmental context in sensitisation research.

These findings add to the growing body of literature implicating DAergic neuroadaptations in the development of sensitisation to drugs of abuse. It has been suggested that these neuroadaptations underlie the development of compulsive drug-taking and drug-seeking behaviour (Robinson & Berridge, 1993). A better understanding of how these neuroadaptations influence behaviour might, therefore, aid in the development of treatments that reverse these neuroadaptations, reducing the compulsive drug-taking and drug-seeking behaviour characteristic of addiction.

References

Aarde, S. M., Miller, M. L., Creehan, K. M., Vandewater, S. A., & Taffe, M. A. (2015). One day access to a running wheel reduces self-administration of D-methamphetamine, MDMA and methylone. *Drug and Alcohol Dependence*, *151*, 151–8. http://doi.org/10.1016/j.drugalcdep.2015.03.016

American Psychiatric Association [APA]. (2000). *DSM-IV. Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.).* APA Publishing.

American Psychiatric Association [APA]. (2013). *DSM-V. Diagnostic and Statistical Manual of Mental Disorders (5th ed.).* APA Publishing.

Aronsen, D., Bukholt, N., & Schenk, S. (2016). Repeated administration of the 5-HT1B/1A agonist, RU 24969, facilitates the acquisition of MDMA self-administration: role of 5-HT1A and 5-HT1B receptor mechanisms. *Psychopharmacology*. http://doi.org/10.1007/s00213-016-4225-x

Ator, N. A., & Griffiths, R. R. (2003). Principles of drug abuse liability assessment in laboratory animals. *Drug and Alcohol Dependence*, *70*(3), S55–S72. http://doi.org/10.1016/S0376-8716(03)00099-1

Australian Institute of Health and Welfare. (2013). *National Drug Strategy Household Survey detailed report: 2013*. Canberra. Retrieved from http://www.aihw.gov.au/publication-detail/?id=60129549469

Ball, K. T., Budreau, D., & Rebec, G. V. (2003). Acute effects of 3,4-methylenedioxymethamphetamine on striatal single-unit activity and behavior in freely moving rats: differential involvement of dopamine D1 and D2 receptors. *Brain Research*, *994*(2), 203–215. http://doi.org/10.1016/j.brainres.2003.09.037

Ball, K. T., Budreau, D., & Rebec, G. V. (2006). Context-dependent behavioural and neuronal sensitization in striatum to MDMA (ecstasy) administration in rats. *The European Journal of Neuroscience*, *24*(1), 217–28. http://doi.org/10.1111/j.1460-9568.2006.04885.x

Ball, K. T., Jarsocrak, H., Hyacinthe, J., Lambert, J., Lockowitz, J., & Schrock, J. (2015). Yohimbine reinstates extinguished 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) seeking in rats with prior exposure to chronic yohimbine. *Behavioural Brain Research*. http://doi.org/10.1016/j.bbr.2015.07.056

Ball, K. T., Klein, J. E., Plocinski, J. A., & Slack, R. (2011). Behavioral sensitization to 3,4-methylenedioxymethamphetamine is long-lasting and modulated by the context of

drug administration. *Behavioural Pharmacology*, *22*(8), 847–50. http://doi.org/10.1097/FBP.0b013e32834d13b4

Ball, K. T., & Rebec, G. V. (2005). Role of 5-HT2A and 5-HT2C/B receptors in the acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on striatal single-unit activity and locomotion in freely moving rats. *Psychopharmacology*, *181*(4), 676–87. http://doi.org/10.1007/s00213-005-0038-z

Ball, K. T., & Slane, M. (2012). Differential involvement of prelimbic and infralimbic medial prefrontal cortex in discrete cue-induced reinstatement of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) seeking in rats. *Psychopharmacology*, *224*(3), 377–85. http://doi.org/10.1007/s00213-012-2762-5

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*, 143–8. http://doi.org/10.1016/j.bbr.2014.08.010

Ball, K. T., Walsh, K. M., & Rebec, G. V. (2007). Reinstatement of MDMA (ecstasy) seeking by exposure to discrete drug-conditioned cues. *Pharmacology, Biochemistry, and Behavior*, *87*(4), 420–5. http://doi.org/10.1016/j.pbb.2007.05.018

Balster, R. L., Kilbey, M. M., & Ellinwood, E. H. (1976). Methamphetamine self-administration in the cat. *Psychopharmacologia*, *46*(3), 229–233. http://doi.org/10.1007/BF00421107

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 : Official Publication of the American College of Neuropsychopharmacology*, *33*(2), 219–25. http://doi.org/10.1038/sj.npp.1301420

Bankson, M. G., & Cunningham, K. A. (2001). 3,4-Methylenedioxymethamphetamine (MDMA) as a Unique Model of Serotonin Receptor Function and Serotonin-Dopamine Interactions. *J. Pharmacol. Exp. Ther.*, *297*(3), 846–852. Retrieved from http://jpet.aspetjournals.org/content/297/3/846.short

Bankson, M. G., & Cunningham, K. A. (2002). Pharmacological studies of the acute effects of (+)-3,4-methylenedioxymethamphetamine on locomotor activity: role of 5-HT(1B/1D) and 5-HT(2) receptors. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *26*(1), 40–52.

http://doi.org/10.1016/S0893-133X(01)00345-1

Barrett, A. C., Miller, J. R., Dohrmann, J. M., & Caine, S. B. (2004). Effects of dopamine indirect agonists and selective D1-like and D2-like agonists and antagonists on cocaine self-administration and food maintained responding in rats. *Neuropharmacology*, *47 Suppl 1*, 256–73. http://doi.org/10.1016/j.neuropharm.2004.07.007

Bassareo, V., & Di Chiara, G. (1999a). Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neuroscience*, *89*(3), 637–641. http://doi.org/10.1016/S0306-4522(98)00583-1

Bassareo, V., & Di Chiara, G. (1999b). Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *European Journal of Neuroscience*, *11*(12), 4389–4397. http://doi.org/10.1046/j.1460-9568.1999.00843.x

Battaglia, G., Brooks, B. P., Kulsakdinun, C., & De Souza, E. B. (1988). Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites. *European Journal of Pharmacology*, *149*(1-2), 159–163. http://doi.org/10.1016/0014-2999(88)90056-8

Battaglia, G., Yeh, S., O'Hearn, E., Molliver, M., Kuhar, M., & De Souza, E. (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. *J. Pharmacol. Exp. Ther.*, *242*(3), 911–916. Retrieved from http://jpet.aspetjournals.org/content/242/3/911.short

Battaglia, G., Yeh, S. Y., & De Souza, E. B. (1988). MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. *Pharmacology, Biochemistry, and Behavior*, *29*(2), 269–74. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2452449

Baumann, M. H., Clark, R. D., Budzynski, A. G., Partilla, J. S., Blough, B. E., & Rothman, R. B. (2005). N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or "Ecstasy"). *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *30*(3), 550–60. http://doi.org/10.1038/sj.npp.1300585

Baumann, M. H., Clark, R. D., Franken, F. H., Rutter, J. J., & Rothman, R. B. (2008).

Tolerance to 3,4-methylenedioxymethamphetamine in rats exposed to single high-dose binges. *Neuroscience*, *152*(3), 773–84. http://doi.org/10.1016/j.neuroscience.2008.01.007

Baumann, M. H., Clark, R. D., & Rothman, R. B. (2008). Locomotor stimulation produced by 3,4-methylenedioxymethamphetamine (MDMA) is correlated with dialysate levels of serotonin and dopamine in rat brain. *Pharmacology, Biochemistry, and Behavior*, *90*(2), 208–17. http://doi.org/10.1016/j.pbb.2008.02.018

Baumann, M. H., Wang, X., & Rothman, R. B. (2007). 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. *Psychopharmacology*, *189*(4), 407–24. http://doi.org/10.1007/s00213-006-0322-6

Beardsley, P. M., Balster, R. L., & Harris, L. S. (1986). Self-administration of methylenedioxymethamphetamine (MDMA) by rhesus monkeys. *Drug and Alcohol Dependence*, *18*(2), 149–157. http://doi.org/10.1016/0376-8716(86)90047-5

Beaulieu, J.-M., & Gainetdinov, R. R. (2011). The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacological Reviews*, *63*(1), 182–217. http://doi.org/10.1124/pr.110.002642

Beck, J. (1990). *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*. (S. J. Peroutka, Ed.) (Vol. 9). Boston, MA: Springer US. http://doi.org/10.1007/978-1-4613-1485-1

Beck, J., & Rosenbaum, M. (1994). *Pursuit of Ecstasy: The MDMA Experience*. SUNY Press. Retrieved from https://books.google.com/books?hl=en&lr=&id=vLiIPBJdY9wC&pgis=1

Bello, E. P., Mateo, Y., Gelman, D. M., Noaín, D., Shin, J. H., Low, M. J., … Rubinstein, M. (2011). Cocaine supersensitivity and enhanced motivation for reward in mice lacking dopamine D2 autoreceptors. *Nature Neuroscience*, *14*(8), 1033–8. http://doi.org/10.1038/nn.2862

Berger, U. V., Gu, X. F., & Azmitia, E. C. (1992). The substituted amphetamines 3,4-methylenedioxymethamphetamine, methamphetamine, p-chloroamphetamine and fenfluramine induce 5-hydroxytryptamine release via a common mechanism blocked by fluoxetine and cocaine. *European Journal of Pharmacology*, *215*(2-3), 153–160. http://doi.org/10.1016/0014-2999(92)90023-W

Bernschneider-Reif, S., Öxler, F., & Freudenmann, R. W. (2006). The origin of MDMA

("Ecstasy") – separating the facts from the myth. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, *61*(11), 966–972. Retrieved from http://www.ingentaconnect.com/content/govi/pharmaz/2006/00000061/00000011/art00015

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*(3), 309–369. http://doi.org/10.1016/S0165-0173(98)00019-8

Bird, J., & Schenk, S. (2013). Contribution of impulsivity and novelty-seeking to the acquisition and maintenance of MDMA self-administration. *Addiction Biology*, *18*(4), 654–64. http://doi.org/10.1111/j.1369-1600.2012.00477.x

Bogen, I. L., Haug, K. H., Myhre, O., & Fonnum, F. (2003). Short- and long-term effects of MDMA ("ecstasy") on synaptosomal and vesicular uptake of neurotransmitters in vitro and ex vivo. *Neurochemistry International*, *43*(4-5), 393–400. http://doi.org/10.1016/S0197-0186(03)00027-5

Boys, A., Marsden, J., & Strang, J. (2001). Understanding reasons for drug use amongst young people: a functional perspective. *Health Education Research*, *16*(4), 457–469. http://doi.org/10.1093/her/16.4.457

Bozarth, M. A., & Wise, R. A. (1986). Involvement of the ventral tegmental dopamine system in opioid and psychomotor stimulant reinforcement. *NIDA Res Monogr*, *67*, 190–196.

Bradbury, S., Bird, J., Colussi-Mas, J., Mueller, M., Ricaurte, G. A., & Schenk, S. (2013). Acquisition of MDMA self-administration: pharmacokinetic factors and MDMA-induced serotonin release. *Addict Biol*, *19*(5), 874–84. http://doi.org/10.1111/adb.12069

Bradbury, S., Gittings, D., & Schenk, S. (2012). Repeated exposure to MDMA and amphetamine: sensitization, cross-sensitization, and response to dopamine D_1- and D_2-like agonists. *Psychopharmacology*, *223*(4), 389–99. http://doi.org/10.1007/s00213-012-2726-9

Braida, D., & Sala, M. (2002). Role of the endocannabinoid system in MDMA intracerebral self-administration in rats. *British Journal of Pharmacology*, *136*(8), 1089–1092. http://doi.org/10.1038/sj.bjp.0704825

Braun, A. R., Laruelle, M., & Mouradian, M. M. (1997). Interactions between D1 and D2 dopamine receptor family agonists and antagonists: the effects of chronic exposure on

behavior and receptor binding in rats and their clinical implications. *Journal of Neural Transmission*, *104*(4-5), 341–362. http://doi.org/10.1007/BF01277656

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.

Brennan, K. A., & Schenk, S. (2006). Initial deficit and recovery of function after MDMA preexposure in rats. *Psychopharmacology*, *184*(2), 239–46. http://doi.org/10.1007/s00213-005-0278-y

Briggs, C. A., Pollock, N. J., Frail, D. E., Paxson, C. L., Rakowski, R. F., Kang, C. H., & Kebabian, J. W. (1991). Activation of the 5-HT1c receptor expressed in Xenopus oocytes by the benzazepines SCH 23390 and SKF 38393. *British Journal of Pharmacology*, *104*(4), 1038–1044. http://doi.org/10.1111/j.1476-5381.1991.tb12546.x

Britton, D. R., Curzon, P., Mackenzie, R. G., Kebabian, J. W., Williams, J. E. G., & Kerkman, D. (1991). Evidence for involvement of both D1 and D2 receptors in maintaining cocaine self-administration. *Pharmacology Biochemistry and Behavior*, *39*(4), 911–915. http://doi.org/10.1016/0091-3057(91)90052-4

Brown, E. R., Jarvie, D. R., & Simpson, D. (1995). Use of drugs at "raves". *Scottish Medical Journal*, *40*(6), 168–71. http://doi.org/10.1177/003693309504000604

Bubar, M. J., Pack, K. M., Frankel, P. S., & Cunningham, K. A. (2004). Effects of dopamine D1- or D2-like receptor antagonists on the hypermotive and discriminative stimulus effects of (+)-MDMA. *Psychopharmacology*, *173*(3-4), 326–36. http://doi.org/10.1007/s00213-004-1790-1

Bull, E. J., Hutson, P. H., & Fone, K. C. . (2004). Decreased social behaviour following 3,4-methylenedioxymethamphetamine (MDMA) is accompanied by changes in 5-HT2A receptor responsivity. *Neuropharmacology*, *46*(2), 202–210. http://doi.org/10.1016/j.neuropharm.2003.08.004

Cabib, S., Castellano, C., Cestari, V., Filibeck, U., & Puglisi-Allegra, S. (1991). D1 and D2 receptor antagonists differently affect cocaine-induced locomotor hyperactivity in the mouse. *Psychopharmacology*, *105*(3), 335–339. http://doi.org/10.1007/BF02244427

Cador, M., Bjijou, Y., & Stinus, L. (1995). Evidence of a complete independence of the

neurobiological substrates for the induction and expression of behavioral sensitization to amphetamine. *Neuroscience*, *65*(2), 385–395. http://doi.org/10.1016/0306-4522(94)00524-9

Caine, S. B., & Koob, G. F. (1994a). Effects of dopamine D-1 and D-2 antagonists on cocaine self- administration under different schedules of reinforcement in the rat. *J. Pharmacol. Exp. Ther.*, *270*(1), 209–218. Retrieved from http://jpet.aspetjournals.org/content/270/1/209.short

Caine, S. B., & Koob, G. F. (1994b). Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. *Journal of the Experimental Analysis of Behavior*, *61*(2), 213–21. http://doi.org/10.1901/jeab.1994.61-213

Callaway, C. W., Rempel, N. L., Peng, R. Y., & Geyer, M. A. (1992). Serotonin 5-HT1-like receptors mediate hyperactivity in rats induced by 3,4-methylenedioxymethamphetamine. *Neuropsychopharmacology*.

Callaway, C. W., Wing, L. L., & Geyer, M. A. (1990). Serotonin release contributes to the locomotor stimulant effects of 3,4- methylenedioxymethamphetamine in rats. *J. Pharmacol. Exp. Ther.*, *254*(2), 456–464. Retrieved from http://jpet.aspetjournals.org/content/254/2/456.short

Camarini, R., & Hodge, C. W. (2004). Ethanol preexposure increases ethanol self-administration in C57BL/6J and DBA/2J mice. *Pharmacology, Biochemistry, and Behavior*, *79*(4), 623–32. http://doi.org/10.1016/j.pbb.2004.09.012

Carlsson, A., Lindqvist, M., Magnusson, T., & Waldeck, B. (1958). On the presence of 3-hydroxytyramine in brain. *Science*, *127*, 471.

Carroll, M. E., & Lac, S. T. (1997). Acquisition of IV amphetamine and cocaine self-administration in rats as a function of dose. *Psychopharmacology*, *129*(3), 206–214. http://doi.org/10.1007/s002130050182

Carroll, M. E., Lac, S. T., Asencio, M., & Kragh, R. (1990a). Fluoxetine reduces intravenous cocaine self-administration in rats. *Pharmacology Biochemistry and Behavior*, *35*(1), 237–244. http://doi.org/10.1016/0091-3057(90)90232-7

Carroll, M. E., Lac, S. T., Asencio, M., & Kragh, R. (1990b). Intravenous cocaine self-administration in rats is reduced by dietaryl-tryptophan. *Psychopharmacology*, *100*(3), 293–300. http://doi.org/10.1007/BF02244596

Carter, L. P., & Griffiths, R. R. (2009). Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug and Alcohol Dependence*,

105 Suppl , S14–25. http://doi.org/10.1016/j.drugalcdep.2009.04.003

Cassidy, G., & Ballard, C. G. (1994). Psychiatric sequelae of MDMA (ecstasy) and related drugs. *Irish Journal of Psychological Medicine*, *11*(03), 132–133. http://doi.org/10.1017/S0790966700014841

Castro, S. W., & Strange, P. G. (1993). Differences in the Ligand Binding Properties of the Short and Long Versions of the D 2 Dopamine Receptor. *Journal of Neurochemistry*, *60*(1), 372–375. http://doi.org/10.1111/j.1471-4159.1993.tb05863.x

Chadwick, I. S., Curry, P. D., Linsley, A., Freemont, A. J., & Doran, B. (1991). Ecstasy, 3-4 methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. *Journal of the Royal Society of Medicine*, *84*(6), 371. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1293290&tool=pmcentrez&rendertype=abstract

Cleary, L., & Docherty, J. R. (2003). Actions of amphetamine derivatives and cathinone at the noradrenaline transporter. *European Journal of Pharmacology*, *476*(1-2), 31–34. http://doi.org/10.1016/S0014-2999(03)02173-3

Cole, J. C., & Sumnall, H. R. (2003). The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA). *Neuroscience & Biobehavioral Reviews*, *27*(3), 199–217. http://doi.org/10.1016/S0149-7634(03)00031-9

Collins, R. J., Weeks, J. R., Cooper, M. M., Good, P. I., & Russell, R. R. (1983). Prediction of abuse liability of drugs using IV self-administration by rats. *Psychopharmacology*, *82*(1-2), 6–13. http://doi.org/10.1007/BF00426372

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. *The European Journal of Neuroscience*, *28*(9), 1895–910. http://doi.org/10.1111/j.1460-9568.2008.06467.x

Colussi-Mas, J., Wise, R. J., Howard, A., & Schenk, S. (2010). Drug seeking in response to a priming injection of MDMA in rats: relationship to initial sensitivity to self-administered MDMA and dorsal striatal dopamine. *Int J Neuropsychopharmacol*, *13*(10), 1315–1327. http://doi.org/10.1017/S1461145710000283

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. *J.*

Pharmacol. Exp. Ther., *241*(1), 338–345. Retrieved from http://jpet.aspetjournals.org/content/241/1/338.short

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*(1-3), 339–341. http://doi.org/10.1016/j.ejphar.2003.09.060

Corrigall, W. A., & Coen, K. M. (1989). Nicotine maintains robust self-administration in rats on a limited-access schedule. *Psychopharmacology*, *99*(4), 473–478. http://doi.org/10.1007/BF00589894

Corrigall, W. A., & Coen, K. M. (1991a). Cocaine self-administration is increased by both D1 and D2 dopamine antagonists. *Pharmacology Biochemistry and Behavior*, *39*(3), 799–802. http://doi.org/10.1016/0091-3057(91)90168-2

Corrigall, W. A., & Coen, K. M. (1991b). Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology*, *104*(2), 171–176. http://doi.org/10.1007/BF02244174

Costall, B., & Naylor, R. J. (1979). Behavioural aspects of dopamine agonists and antagonists. In *The neurobiology of dopamine* (pp. 555–576). Academic Press London.

Cottler, L. B., Leung, K. S., & Abdallah, A. Ben. (2009). Test-re-test reliability of DSM-IV adopted criteria for 3,4-methylenedioxymethamphetamine (MDMA) abuse and dependence: a cross-national study. *Addiction (Abingdon, England)*, *104*(10), 1679–90. http://doi.org/10.1111/j.1360-0443.2009.02649.x

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.

Crawley, J. N. (1985). Exploratory behavior models of anxiety in mice. *Neuroscience & Biobehavioral Reviews*, *9*(1), 37–44. http://doi.org/10.1016/0149-7634(85)90030-2

Creehan, K. M., Vandewater, S. A., & Taffe, M. A. (2015). Intravenous self-administration of mephedrone, methylone and MDMA in female rats. *Neuropharmacology*, *92*, 90–7. http://doi.org/10.1016/j.neuropharm.2015.01.003

Crespi, D., Mennini, T., & Gobbi, M. (1997). Carrier-dependent and Ca(2+)-dependent 5-HT and dopamine release induced by (+)-amphetamine, 3,4-

methylendioxymethamphetamine, p-chloroamphetamine and (+)-fenfluramine. *British Journal of Pharmacology*, *121*(8), 1735–43. http://doi.org/10.1038/sj.bjp.0701325

Criswell, H. (1983). Intravenous self-administration of morphine by naive mice. *Pharmacology Biochemistry and Behavior*, *18*(3), 467–470. http://doi.org/10.1016/0091-3057(83)90471-9

Czoty, P. W., Ginsburg, B. C., & Howell, L. L. (2002). Serotonergic Attenuation of the Reinforcing and Neurochemical Effects of Cocaine in Squirrel Monkeys. *Journal of Pharmacology and Experimental Therapeutics*, *300*(3), 831–837. http://doi.org/10.1124/jpet.300.3.831

Dalley, J. W., Lääne, K., Theobald, D. E. H., Peña, Y., Bruce, C. C., Huszar, A. C., … Robbins, T. W. (2007). Enduring deficits in sustained visual attention during withdrawal of intravenous methylenedioxymethamphetamine self-administration in rats: results from a comparative study with d-amphetamine and methamphetamine. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *32*(5), 1195–206. http://doi.org/10.1038/sj.npp.1301220

Daniela, E., Brennan, K. A., 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), 745–50. http://doi.org/10.1016/j.pbb.2004.01.008

Daniela, E., Gittings, D., & Schenk, S. (2006). Conditioning Following Repeated Exposure to MDMA in Rats: Role in the Maintenance of MDMA Self-Administration. *Behav Neurosci*, *120*(5), 1144. Retrieved from http://search.proquest.com/docview/203900307?accountid=14782

De La Garza, R., Fabrizio, K. R., & Gupta, A. (2007). Relevance of rodent models of intravenous MDMA self-administration to human MDMA consumption patterns. *Psychopharmacology*, *189*(4), 425–34. http://doi.org/10.1007/s00213-005-0255-5

de la Torre, R., & Farré, M. (2004). Neurotoxicity of MDMA (ecstasy): the limitations of scaling from animals to humans. *Trends in Pharmacological Sciences*, *25*(10), 505–8. http://doi.org/10.1016/j.tips.2004.08.001

De Vries, T. J., Schoffelmeer, A. N. M., Binnekade, R., & Vanderschuren, L. J. M. J. (1999). Dopaminergic mechanisms mediating the incentive to seek cocaine and heroin following long-term withdrawal of IV drug self-administration.

Psychopharmacology, *143*(3), 254–260. http://doi.org/10.1007/s002130050944

Degenhardt, L., Barker, B., & Topp, L. (2004). Patterns of ecstasy use in Australia: findings from a national household survey. *Addiction*, *99*(2), 187–195. http://doi.org/10.1111/j.1360-0443.2003.00622.x

Degenhardt, L., Whiteford, H. A., Ferrari, A. J., Baxter, A. J., Charlson, F. J., Hall, W. D., … Vos, T. (2013). Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet (London, England)*, *382*(9904), 1564–74. http://doi.org/10.1016/S0140-6736(13)61530-5

Deneau, G., Yanagita, T., & Seevers, M. H. (1969). Self-administration of psychoactive substances by the monkey. *Psychopharmacologia*, *16*(1), 30–48. http://doi.org/10.1007/BF00405254

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. http://doi.org/10.1073/pnas.85.14.5274

Di Matteo, V., Di Giovanni, G., Pierucci, M., & Esposito, E. (2008). Serotonin control of central dopaminergic function: focus on in vivo microdialysis studies. *Progress in Brain Research*, *172*, 7–44. http://doi.org/10.1016/S0079-6123(08)00902-3

Dianna, S. L., Smith, F. L., Smith, D. G., & Lyness, W. H. (1986). Fluoxetine-induced attenuation of amphetamine self-administration in rats. *Life Sciences*, *39*(15), 1383–1388.

Do, J., & Schenk, S. (2013). Self-administered MDMA produces dose- and time-dependent serotonin deficits in the rat brain. *Addiction Biology*, *18*(3), 441–7. http://doi.org/10.1111/j.1369-1600.2011.00370.x

Downing, J. (1986). The psychological and physiological effects of MDMA on normal volunteers. *Journal of Psychoactive Drugs*, *18*(4), 335–40. http://doi.org/10.1080/02791072.1986.10472366

Downs, A. W., & Eddy, N. B. (1932a). The effect of repeated doses of cocaine on the dog. *Journal of Pharmacology and Experimental Therapeutics*, *46*(2), 195–198.

Downs, A. W., & Eddy, N. B. (1932b). The effect of repeated doses of cocaine on the rat. *Journal of Pharmacology and Experimental Therapeutics*, *46*(2), 199–200.

Dworkin, S., Guerin, G., Co, C., Smith, J. E., & Goeders, N. (1988). Effects of 5,7-

dihydroxytryptamine lesions of the nucleus accumbens in rats responding on a concurrent schedule of food, water and intravenous morphine self-administration. *NIDA Research Monograph*, *81*, 149–55. Retrieved from http://europepmc.org/abstract/med/3136354

Dykhuizen, R. S., Brunt, P. W., Atkinson, P., Simpson, J. G., & Smith, C. C. (1995). Ecstasy induced hepatitis mimicking viral hepatitis. *Gut*, *36*(6), 939–941. http://doi.org/10.1136/gut.36.6.939

Eiden, L. E., & Weihe, E. (2011). VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. *Annals of the New York Academy of Sciences*, *1216*, 86–98. http://doi.org/10.1111/j.1749-6632.2010.05906.x

Eilam, D., Clements, K. V. A., & Szechtman, H. (1991). Differential effects of D1 and D2 dopamine agonists on stereotyped locomotion in rats. *Behavioural Brain Research*, *45*(2), 117–124. http://doi.org/10.1016/S0166-4328(05)80077-4

Eilam, D., Golani, I., & Szechtman, H. (1989). D2-agonist quinpirole induces perseveration of routes and hyperactivity but no perseveration of movements. *Brain Research*, *490*(2), 255–267. http://doi.org/10.1016/0006-8993(89)90243-6

Eilam, D., & Szechtman, H. (1989). Biphasic effect of D-2 agonist quinpirole on locomotion and movements. *European Journal of Pharmacology*, *161*(2-3), 151–157. http://doi.org/10.1016/0014-2999(89)90837-6

Engels, R. C. M. E., & ter Bogt, T. (2004). Outcome expectancies and ecstasy use in visitors of rave parties in The Netherlands. *European Addiction Research*, *10*(4), 156–62. http://doi.org/10.1159/000079836

Ennaceur, A., Michalikova, S., & Chazot, P. L. (2006). Models of anxiety: responses of rats to novelty in an open space and an enclosed space. *Behavioural Brain Research*, *171*(1), 26–49. http://doi.org/10.1016/j.bbr.2006.03.016

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), 356–64. http://doi.org/10.1007/s00213-002-1021-6

Fantegrossi, W. E., Woolverton, W. L., Kilbourn, M., Sherman, P., Yuan, J., Hatzidimitriou, G., … Winger, G. (2004). Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. *Neuropsychopharmacology*, *29*(7), 1270–1281.

Feduccia, A. A., Kongovi, N., & Duvauchelle, C. L. (2010). Heat increases MDMA-enhanced NAcc 5-HT and body temperature, but not MDMA self-administration. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *20*(12), 884–94. http://doi.org/10.1016/j.euroneuro.2010.08.009

File, S. E. (2001). Factors controlling measures of anxiety and responses to novelty in the mouse. *Behavioural Brain Research*, *125*(1-2), 151–157. http://doi.org/10.1016/S0166-4328(01)00292-3

Fineschi, V., & Masti, A. (1996). Fatal poisoning by MDMA (ecstasy) and MDEA: A case report. *International Journal of Legal Medicine*, *108*(5), 272–275. http://doi.org/10.1007/BF01369826

Fiorino, D. F., Coury, A., & Phillips, A. G. (1997). Dynamic Changes in Nucleus Accumbens Dopamine Efflux During the Coolidge Effect in Male Rats. *J. Neurosci.*, *17*(12), 4849–4855. Retrieved from http://www.jneurosci.org/content/17/12/4849.short

Fitzgerald, J. L., & Reid, J. J. (1990). Effects of methylenedioxymethamphetamine on the release of monoamines from rat brain slices. *European Journal of Pharmacology*, *191*(2), 217–220. http://doi.org/10.1016/0014-2999(90)94150-V

Fitzgerald, R. L., Blanke, R. V, & Poklis, A. (1990). Stereoselective pharmacokinetics of 3,4-methylenedioxymethamphetamine in the rat. *Chirality*, *2*(4), 241–8. http://doi.org/10.1002/chir.530020409

Fleckenstein, A. E., Brown, J. M., Sandoval, V., Riddle, E. L., Hansen, J. P., Ugarte, Y. V, … Hanson, G. R. (2002). D2 receptor-mediated regulation of vesicular dopamine uptake. In *Catecholamine Research* (pp. 39–42). Springer.

Fletcher, P. J., Korth, K. M., & Chambers, J. W. (1999). Selective destruction of brain serotonin neurons by 5,7-dihydroxytryptamine increases responding for a conditioned reward. *Psychopharmacology*, *147*(3), 291–299. http://doi.org/10.1007/s002130051170

Fletcher, P. J., Robinson, S. R., & Slippoy, D. L. (2001). Pre-exposure to (+/-)3,4-methylenedioxy-methamphetamine (MDMA) facilitates acquisition of intravenous cocaine self-administration in rats. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *25*(2), 195–203. http://doi.org/10.1016/S0893-133X(01)00222-6

Fletcher, P. J., Sinyard, J., & Higgins, G. A. (2006). The effects of the 5-HT(2C) receptor antagonist SB242084 on locomotor activity induced by selective, or mixed, indirect serotonergic and dopaminergic agonists. *Psychopharmacology*, *187*(4), 515–25. http://doi.org/10.1007/s00213-006-0453-9

Fone, K. C. F., Beckett, S. R. G., Topham, I. A., Swettenham, J., Ball, M., & Maddocks, L. (2002). Long-term changes in social interaction and reward following repeated MDMA administration to adolescent rats without accompanying serotonergic neurotoxicity. *Psychopharmacology*, *159*(4), 437–44. http://doi.org/10.1007/s00213-001-0931-z

Food and Drug Administration. (2010). *Guidance for Industry: Assessment of Abuse Potential of Drugs*. Retrieved from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

Freedman, R. R., Johanson, C.-E., & Tancer, M. E. (2005). Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology*, *183*(2), 248–56. http://doi.org/10.1007/s00213-005-0149-6

Freudenmann, R. W., Oxler, F., & Bernschneider-Reif, S. (2006). The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. *Addiction (Abingdon, England)*, *101*(9), 1241–5. http://doi.org/10.1111/j.1360-0443.2006.01511.x

García-Repetto, R., Moreno, E., Soriano, T., Jurado, C., Giménez, M. P., & Menéndez, M. (2003). Tissue concentrations of MDMA and its metabolite MDA in three fatal cases of overdose. *Forensic Science International*, *135*(2), 110–114. http://doi.org/10.1016/S0379-0738(03)00179-8

Gentsch, C., Lichtsteiner, M., Frischknecht, H.-R., Feer, H., & Siegfried, B. (1988). Isolation-induced locomotor hyperactivity and hypoalgesia in rats are prevented by handling and reversed by resocialization. *Physiology & Behavior*, *43*(1), 13–16. http://doi.org/10.1016/0031-9384(88)90091-1

Gerber, G. J., & Stretch, R. (1975). Drug-induced reinstatement of extinguished self-administration behavior in monkeys. *Pharmacology Biochemistry and Behavior*, *3*(6), 1055–1061. http://doi.org/10.1016/0091-3057(75)90016-7

Geyer, M. A., Russo, P. V., & Masten, V. L. (1986). Multivariate assessment of locomotor behavior: Pharmacological and behavioral analyses. *Pharmacology Biochemistry and*

Behavior, *25*(1), 277–288. http://doi.org/10.1016/0091-3057(86)90266-2

Goeders, N., & Smith, J. E. (1983). Cortical dopaminergic involvement in cocaine reinforcement. *Science*, *221*(4612), 773–775. http://doi.org/10.1126/science.6879176

Gold, L. H., Hubner, C. B., & Koob, G. F. (1989). A role for the mesolimbic dopamine system in the psychostimulant actions of MDMA. *Psychopharmacology*, *99*(1), 40–47. http://doi.org/10.1007/BF00634450

Gold, L. H., & Koob, G. F. (1988). Methysergide potentiates the hyperactivity produced by MDMA in rats. *Pharmacology Biochemistry and Behavior*, *29*(3), 645–648. http://doi.org/10.1016/0091-3057(88)90034-2

Gold, L. H., Koob, G. F., & Geyer, M. A. (1990). Spatial pattern analysis reveals similarities between amphetamine conditioned and unconditioned locomotion. *Behav Pharmacol*, *1*(3), 209–220. Retrieved from http://journals.lww.com/behaviouralpharm/Fulltext/1990/00130/Spatial_pattern_analysis_reveals_similarities.3.aspx

Gold, L. H., Koob, G., & Geyer, M. (1988). Stimulant and hallucinogenic behavioral profiles of 3,4- methylenedioxymethamphetamine and N-ethyl-3,4-methylenedioxyamphetamine in rats. *J. Pharmacol. Exp. Ther.*, *247*(2), 547–555. Retrieved from http://jpet.aspetjournals.org/content/247/2/547.short

Goldberg, S. R., Hoffmeister, F., Schlichting, U. U., & Wuttke, W. (1971). A COMPARISON OF PENTOBARBITAL AND COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS: EFFECTS OF DOSE AND FIXED-RATIO PARAMETER. *J. Pharmacol. Exp. Ther.*, *179*(2), 277–283. Retrieved from http://jpet.aspetjournals.org/content/179/2/277.short

Goldberg, S. R., Woods, J. H., & Schuster, C. R. (1971). NALORPHINE-INDUCED CHANGES IN MORPHINE SELF-ADMINISTRATION IN RHESUS MONKEYS. *J. Pharmacol. Exp. Ther.*, *176*(2), 464–471. Retrieved from http://jpet.aspetjournals.org/content/176/2/464.short

Götestam, K. G., & Andersson, B. E. (1975). Self-administration of amphetamine analogues in rats. *Pharmacology, Biochemistry, and Behavior*, *3*(2), 229–33. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1170576

Gould, R. W., Gage, H. D., Banks, M. L., Blaylock, B. L., Czoty, P. W., & Nader, M. A. (2011). Differential effects of cocaine and MDMA self-administration on cortical serotonin transporter availability in monkeys. *Neuropharmacology*, *61*(1-2), 245–51.

http://doi.org/10.1016/j.neuropharm.2011.04.007

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. http://doi.org/10.1124/pr.55.3.3

Griffiths, R. R., Brady, J. V, & Bradford, L. D. (1979). Predicting the abuse liability of drugs with animal drug self-administration procedures: Psychomotor stimulants and hallucinogens. *Advances in Behavioral Pharmacology*, *2*, 163–208.

Grove, R. N., & Schuster, C. R. (1974). Suppression of cocaine self-administration by extinction and punishment. *Pharmacology Biochemistry and Behavior*, *2*(2), 199–208. http://doi.org/10.1016/0091-3057(74)90053-7

Gu, X. F., & Azmitia, E. C. (1993). Integrative transporter-mediated release from cytoplasmic and vesicular 5-hydroxytryptamine stores in cultured neurons. *European Journal of Pharmacology*, *235*(1), 51–57. http://doi.org/10.1016/0014-2999(93)90819-4

Gudelsky, G. A., & Nash, J. F. (2002). Carrier-Mediated Release of Serotonin by 3,4-Methylenedioxymethamphetamine: Implications for Serotonin-Dopamine Interactions. *Journal of Neurochemistry*, *66*(1), 243–249. http://doi.org/10.1046/j.1471-4159.1996.66010243.x

Gudelsky, G. A., & Yamamoto, B. K. (2008). Actions of 3,4-methylenedioxymethamphetamine (MDMA) on cerebral dopaminergic, serotonergic and cholinergic neurons. *Pharmacology, Biochemistry, and Behavior*, *90*(2), 198–207. http://doi.org/10.1016/j.pbb.2007.10.003

Halpern, J. H., Pope, H. G., Sherwood, A. R., Barry, S., Hudson, J. I., & Yurgelun-Todd, D. (2004). Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug and Alcohol Dependence*, *75*(2), 135–47. http://doi.org/10.1016/j.drugalcdep.2004.02.008

Hamamura, T., Akiyama, K., Akimoto, K., Kashihara, K., Okumura, K., Ujike, H., & Otsuki, S. (1991). Co-administration of either a selective D1 or D2 dopamine antagonist with methamphetamine prevents methamphetamine-induced behavioral sensitization and neurochemical change, studied by in vivo intracerebral dialysis. *Brain Research*, *546*(1), 40–46. http://doi.org/10.1016/0006-8993(91)91156-U

Hammersley, R. (1999). Patterns of ecstasy use by drug users. *British Journal of Criminology*, *39*(4), 625–647. http://doi.org/10.1093/bjc/39.4.625

Hansen, D., Maycock, B., & Lower, T. (2001). "Weddings, parties, anything…", a qualitative analysis of ecstasy use in Perth, Western Australia. *International Journal of Drug Policy*, *12*(2), 181–199. http://doi.org/10.1016/S0955-3959(00)00075-X

Hardman, H. F., Haavik, C. O., & Seevers, M. H. (1973). Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. *Toxicology and Applied Pharmacology*, *25*(2), 299–309. http://doi.org/10.1016/S0041-008X(73)80016-X

Harkin, A. (2000). Test Conditions Influence the Response to a Drug Challenge in Rodents. *Pharmacology Biochemistry and Behavior*, *65*(3), 389–398. http://doi.org/10.1016/S0091-3057(99)00210-5

Hekmatpanah, C. R., & Peroutka, S. J. (1990). 5-Hydroxytryptamine uptake blockers attenuate the 5-hydroxytryptamine-releasing effect of 3,4-methylenedioxymethamphetamine and related agents. *European Journal of Pharmacology*, *177*(1-2), 95–98. http://doi.org/10.1016/0014-2999(90)90555-K

Herin, D. V, Liu, S., Ullrich, T., Rice, K. C., & Cunningham, K. A. (2005). Role of the serotonin 5-HT2A receptor in the hyperlocomotive and hyperthermic effects of (+)-3,4-methylenedioxymethamphetamine. *Psychopharmacology*, *178*(4), 505–13. http://doi.org/10.1007/s00213-004-2030-4

Higgins, G. A., Wang, Y., Corrigall, W. A., & Sellers, E. M. (1994). Influence of 5-HT3 receptor antagonists and the indirect 5-HT agonist, dexfenfluramine, on heroin self-administration in rats. *Psychopharmacology*, *114*(4), 611–619. http://doi.org/10.1007/BF02244992

Hillegaart, V. (1990). Effects of local application of 5-HT and 8-OH-DPAT into the dorsal and median raphe nuclei on motor activity in the rat. *Physiology & Behavior*, *48*(1), 143–148. http://doi.org/10.1016/0031-9384(90)90275-9

Hillegaart, V., Estival, A., & Ahlenius, S. (1996). Evidence for specific involvement of 5-HT1A and receptors in the expression of patterns of spontaneous motor activity of the rat. *European Journal of Pharmacology*, *295*(2-3), 155–161. http://doi.org/10.1016/0014-2999(95)00666-4

Hillegaart, V., Wadenberg, M.-L., & Ahlenius, S. (1989). Effects of 8-OH-DPAT on motor activity in the rat. *Pharmacology Biochemistry and Behavior*, *32*(3), 797–800.

http://doi.org/10.1016/0091-3057(89)90036-1

Hoffman, D. C., & Beninger, R. J. (1985). The D1 dopamine receptor antagonist, SCH 23390 reduces locomotor activity and rearing in rats. *Pharmacology Biochemistry and Behavior*, *22*(2), 341–342. http://doi.org/10.1016/0091-3057(85)90401-0

Hondebrink, L., Meulenbelt, J., Meijer, M., van den Berg, M., & Westerink, R. H. S. (2011). High concentrations of MDMA (’ecstasy') and its metabolite MDA inhibit calcium influx and depolarization-evoked vesicular dopamine release in PC12 cells. *Neuropharmacology*, *61*(1-2), 202–8. http://doi.org/10.1016/j.neuropharm.2011.03.028

Hopper, J. W., Su, Z., Looby, A. R., Ryan, E. T., Penetar, D. M., Palmer, C. M., & Lukas, S. E. (2006). Incidence and patterns of polydrug use and craving for ecstasy in regular ecstasy users: an ecological momentary assessment study. *Drug and Alcohol Dependence*, *85*(3), 221–35. http://doi.org/10.1016/j.drugalcdep.2006.04.012

Horger, B. A., Giles, M. K., & Schenk, S. (1992). Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. *Psychopharmacology*, *107*(2-3), 271–276. http://doi.org/10.1007/BF02245147

Horger, B. A., Shelton, K., & Schenk, S. (1990). Preexposure sensitizes rats to the rewarding effects of cocaine. *Pharmacology Biochemistry and Behavior*, *37*(4), 707–711. http://doi.org/10.1016/0091-3057(90)90552-S

Horger, B. A., Wellman, P. J., Morien, A., Davies, B. T., & Schenk, S. (1991). Caffeine exposure sensitizes rats to the reinforcing effects of cocaine. *Neuroreport*, *2*(1), 53–56.

Hornykiewicz, O. (1966). DOPAMINE (3-HYDROXYTYRAMINE) AND BRAIN FUNCTION. *Pharmacol. Rev.*, *18*(2), 925–964. Retrieved from http://pharmrev.aspetjournals.org/content/18/2/925.short

Howell, L. L., & Byrd, L. D. (1991). Characterization of the effects of cocaine and GBR 12909, a dopamine uptake inhibitor, on behavior in the squirrel monkey. *J. Pharmacol. Exp. Ther.*, *258*(1), 178–185. Retrieved from http://jpet.aspetjournals.org/content/258/1/178.short

Howell, L. L., & Byrd, L. D. (1995). Serotonergic modulation of the behavioral effects of cocaine in the squirrel monkey. *Journal of Pharmacology and Experimental Therapeutics*, *275*(3), 1551–1559. Retrieved from http://jpet.aspetjournals.org/content/275/3/1551.abstract

Hubner, C. B., & Edward Moreton, J. (1991). Effects of selective D1 and D2 dopamine antagonists on cocaine self-administration in the rat. *Psychopharmacology*, *105*(2), 151–156. http://doi.org/10.1007/BF02244301

Hurd, Y. L., Weiss, F., Koob, G. F., And, N.-E., & Ungerstedt, U. (1989). Cocaine reinforcement and extracellular dopamine overflow in rat nucleus accumbens: an in vivo microdialysis study. *Brain Research*, *498*(1), 199–203. http://doi.org/10.1016/0006-8993(89)90422-8

Hysek, C. M., Simmler, L. D., Ineichen, M., Grouzmann, E., Hoener, M. C., Brenneisen, R., … Liechti, M. E. (2011). The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("ecstasy") in humans. *Clinical Pharmacology and Therapeutics*, *90*(2), 246–55. http://doi.org/10.1038/clpt.2011.78

Insel, T., Battaglia, G., Johannessen, J., Marra, S., & De Souza, E. (1989). 3,4-Methylenedioxymethamphetamine ("ecstasy") selectively destroys brain serotonin terminals in rhesus monkeys. *J. Pharmacol. Exp. Ther.*, *249*(3), 713–720. Retrieved from http://jpet.aspetjournals.org/content/249/3/713.short

Iravani, M. M., Asari, D., Patel, J., Wieczorek, W. J., & Kruk, Z. L. (2000). Direct effects of 3,4-methylenedioxymethamphetamine (MDMA) on serotonin or dopamine release and uptake in the caudate putamen, nucleus accumbens, substantia nigra pars reticulata, and the dorsal raphé nucleus slices. *Synapse (New York, N.Y.)*, *36*(4), 275–85. http://doi.org/10.1002/(SICI)1098-2396(20000615)36:4<275::AID-SYN4>3.0.CO;2-#

Jansen, K. (1997). Adverse psychological effects of ecstasy use and their treatment. *Ecstasy Reconsidered*, 112–128.

Jansen, K. (1999). Ecstasy (MDMA) dependence. *Drug and Alcohol Dependence*, *53*(2), 121–124. http://doi.org/10.1016/S0376-8716(98)00111-2

Johnson, M. P., Hoffman, A. J., & Nichols, D. E. (1986). Effects of enantiomers of MDA, MDMA and related analogues on [3H]serotonin and [3H]dopamine release from superfused rat brain slices. *European Journal of Pharmacology*, *132*(2-3), 269–276. http://doi.org/10.1016/0014-2999(86)90615-1

Johnston, L. (2010). *Monitoring the Future: National Results on Adolescent Drug Use: Overview of Key Findings*. DIANE Publishing. Retrieved from https://books.google.com/books?hl=en&lr=&id=rea9HJO0_UEC&pgis=1

Jones, K., Brennan, K. A., Colussi-Mas, J., & Schenk, S. (2010). Tolerance to 3,4-

methylenedioxymethamphetamine is associated with impaired serotonin release. *Addiction Biology*, *15*(3), 289–98. http://doi.org/10.1111/j.1369-1600.2010.00217.x

Kalivas, P. W., Duffy, P., & White, S. R. (1998). MDMA elicits behavioral and neurochemical sensitization in rats. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *18*(6), 469–79. http://doi.org/10.1016/S0893-133X(97)00195-4

Kalivas, P. W., Nemeroff, C. B., & Prange, A. J. (1984). Neurotensin microinjection into the nucleus accumbens antagonizes dopamine-induced increase in locomotion and rearing. *Neuroscience*, *11*(4), 919–930. http://doi.org/10.1016/0306-4522(84)90203-3

Kalivas, P. W., & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Research Reviews*, *16*(3), 223–244. http://doi.org/10.1016/0165-0173(91)90007-U

Kalivas, P. W., & Weber, B. (1988). Amphetamine injection into the ventral mesencephalon sensitizes rats to peripheral amphetamine and cocaine. *J. Pharmacol. Exp. Ther.*, *245*(3), 1095–1102. Retrieved from http://jpet.aspetjournals.org/content/245/3/1095.abstract?ijkey=c6effe0175b373f3c975b52b955062d1da3ee8d4&keytype2=tf_ipsecsha

Kebabian, J. W., & Calne, D. B. (1979). Multiple receptors for dopamine. *Nature*, *277*(5692), 93–96.

Kehne, J. H., Ketteler, H. J., McCloskey, T. C., Sullivan, C. K., Dudley, M. W., & Schmidt, C. J. (1996). Effects of the selective 5-HT2A receptor antagonist MDL 100,907 on MDMA-induced locomotor stimulation in rats. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *15*(2), 116–24. http://doi.org/10.1016/0893-133X(95)00160-F

Khakoo, S. I., Coles, C. J., Armstrong, J. S., & Barry, R. E. (1995). Hepatotoxicity and accelerated fibrosis following 3, 4-methylenedioxymetamphetamine (“ ecstasy”) usage. *Journal of Clinical Gastroenterology*, *20*(3), 244–247.

Kivell, B., Day, D., Bosch, P., Schenk, S., & Miller, J. (2010). MDMA causes a redistribution of serotonin transporter from the cell surface to the intracellular compartment by a mechanism independent of phospho-p38-mitogen activated protein kinase activation. *Neuroscience*, *168*(1), 82–95. http://doi.org/10.1016/j.neuroscience.2010.03.018

Kleven, M. S., Woolverton, W. L., & Seiden, L. S. (1989). Evidence that both intragastric and subcutaneous administration of methylenedioxymethylamphetamine (MDMA) produce serotonin neurotoxicity in rhesus monkeys. *Brain Research*, *488*(1-2), 121–125. http://doi.org/10.1016/0006-8993(89)90700-2

Koob, G. F. (1992). Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Sciences*, *13*, 177–184. http://doi.org/10.1016/0165-6147(92)90060-J

Koob, G. F., Le, H. T., & Creese, I. (1987). The D1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. *Neuroscience Letters*, *79*(3), 315–320. http://doi.org/10.1016/0304-3940(87)90451-4

Kuribara, H. (1995). Inhibition of methamphetamine sensitization by post-methamphetamine treatment with SCH 23390 or haloperidol. *Psychopharmacology*, *119*(1), 34–38. http://doi.org/10.1007/BF02246051

Kuribara, H. (1996). Effects of Sulpiride and Nemonapride, Benzamide Derivatives Having Distinct Potencies of Antagonistic Action on Dopamine D2 Receptors, on Sensitization to Methamphetamine in Mice. *Journal of Pharmacy and Pharmacology*, *48*(3), 292–296. http://doi.org/10.1111/j.2042-7158.1996.tb05919.x

Kuribara, H., & Uchihashi, Y. (1993). Dopamine Antagonists Can Inhibit Methamphetamine Sensitization, But Not Cocaine Sensitization, When Assessed by Ambulatory Activity in Mice. *Journal of Pharmacy and Pharmacology*, *45*(12), 1042–1045. http://doi.org/10.1111/j.2042-7158.1993.tb07177.x

Kuribara, H., & Uchihashi, Y. (1994). Effects of dopamine antagonism on methamphetamine sensitization: Evaluation by ambulatory activity in mice. *Pharmacology Biochemistry and Behavior*, *47*(1), 101–106. http://doi.org/10.1016/0091-3057(94)90117-1

LaHoste, G. J., & Marshall, J. F. (1991). Chronic eticlopride and dopamine denervation induce equal nonadditive increases in striatal D2 receptor density: autoradiographic evidence against the dual mechanism hypothesis. *Neuroscience*, *41*(2-3), 473–81. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1678501

Lamb, R. J., & Griffiths, R. R. (1987). Self-injection of d,1-3,4-methylenedioxymethamphetamine (MDMA) in the baboon. *Psychopharmacology*, *91*(3), 268–272. http://doi.org/10.1007/BF00518175

Lamb, R. J., & Griffiths, R. R. (1990). Self-administration in baboons and the

discriminative stimulus effects in rats of bupropion, nomifensine, diclofensine and imipramine. *Psychopharmacology*, *102*(2), 183–190. http://doi.org/10.1007/BF02245920

Lawn, J. C. (1985). Schedules of controlled substances: Temporary placement of 3, 4-methylenedioxymethamphetamine (MDMA) into Schedule I. *Federal Register*, *50*(105), 23118–23120.

Leccese, A. P., & Lyness, W. H. (1984). The effects of putative 5-hydroxytryptamine receptor active agents ond-amphetamine self-administration in controls and rats with 5,7-dihydroxytryptamine median forebrain bundle lesion. *Brain Research*, *303*(1), 153–162. http://doi.org/10.1016/0006-8993(84)90223-3

Lenton, S., Boys, A., & Norcross, K. (1997). Raves, drugs and experience: drug use by a sample of people who attend raves in Western Australia. *Addiction*, *92*(10), 1327–1337. http://doi.org/10.1111/j.1360-0443.1997.tb02851.x

Leonardi, E. T., & Azmitia, E. C. (1994). MDMA (ecstasy) inhibition of MAO type A and type B: comparisons with fenfluramine and fluoxetine (Prozac). *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *10*(4), 231–8. http://doi.org/10.1038/npp.1994.26

Liechti, M. E., Gamma, A., & Vollenweider, F. X. (2001). Gender differences in the subjective effects of MDMA. *Psychopharmacology*, *154*(2), 161–168. http://doi.org/10.1007/s002130000648

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. http://doi.org/10.1016/j.drugalcdep.2004.10.006

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., … Memish, Z. A. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, *380*(9859), 2224–60. http://doi.org/10.1016/S0140-6736(12)61766-8

Lorrain, D. S., Arnold, G. M., & Vezina, P. (2000). Previous exposure to amphetamine increases incentive to obtain the drug: long-lasting effects revealed by the progressive ratio schedule. *Behavioural Brain Research*, *107*(1-2), 9–19. http://doi.org/10.1016/S0166-4328(99)00109-6

Ludwig, V., Mihov, Y., & Schwarting, R. K. W. (2008). Behavioral and neurochemical consequences of multiple MDMA administrations in the rat: Role of individual differences in anxiety-related behavior. *Behavioural Brain Research*, *189*(1), 52–64. http://doi.org/10.1016/j.bbr.2007.12.008

Lyness, W. H. (1983). Effect of L-tryptophan pretreatment on d-amphetamine self administration. *Substance & Alcohol Actions/Misuse*.

Lyness, W. H., Friedle, N. ., & Moore, K. . (1980). Increased self-administration of d-amphetamine after destruction of 5-hydroxytryptaminergic neurons. *Pharmacology Biochemistry and Behavior*, *12*(6), 937–941. http://doi.org/10.1016/0091-3057(80)90456-6

Lyness, W. H., Friedle, N. M., & Moore, K. E. (1979). Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on d-amphetamine self-administration. *Pharmacology Biochemistry and Behavior*, *11*(5), 553–556. http://doi.org/10.1016/0091-3057(79)90040-6

Lyness, W. H., & Smith, J. E. (1992). Influence of dopaminergic and serotonergic neurons on intravenous ethanol self-administration in the rat. *Pharmacology, Biochemistry, and Behavior*, *42*(1), 187–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1388276

Malmberg, A., Jackson, D. M., Eriksson, A., & Mohell, N. (1993). Unique binding characteristics of antipsychotic agents interacting with human dopamine D2A, D2B, and D3 receptors. *Mol. Pharmacol.*, *43*(5), 749–754. Retrieved from http://molpharm.aspetjournals.org/content/43/5/749.short

Maura, G., Gemignani, A., Versace, P., Martire, M., & Raiteri, M. (1982). Carrier-mediated and carrier-independent release of serotonin from isolated central nerve endings. *Neurochemistry International*, *4*(4), 219–224. http://doi.org/10.1016/0197-0186(82)90057-2

Mayerhofer, A., Kovar, K.-A., & Schmidt, W. J. (2001). Changes in serotonin, dopamine and noradrenaline levels in striatum and nucleus accumbens after repeated administration of the abused drug MDMA in rats. *Neuroscience Letters*, *308*(2), 99–102. http://doi.org/10.1016/S0304-3940(01)01992-9

McCann, U. D., Ridenour, A., Shaham, Y., & Ricaurte, G. A. (1994). Serotonin neurotoxicity after (+/-)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): a controlled study in humans. *Neuropsychopharmacology : Official Publication of the*

American College of Neuropsychopharmacology, *10*(2), 129–38. http://doi.org/10.1038/npp.1994.15

McCann, U. D., Szabo, Z., Scheffel, U., Dannals, R., & 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. http://doi.org/10.1016/S0140-6736(98)04329-3

McCreary, A. C., Bankson, M. G., & Cunningham, K. A. (1999). Pharmacological studies of the acute and chronic effects of (+)-3, 4-methylenedioxymethamphetamine on locomotor activity: role of 5-hydroxytryptamine1A and 5-hydroxytryptamine1B/1D receptors. *Journal of Pharmacology and Experimental Therapeutics*, *290*(3), 965–973. Retrieved from http://jpet.aspetjournals.org/content/290/3/965.short

McDowell, D. M., & Kleber, H. D. (1994). MDMA: its history and pharmacology. *Psychiatric Annals*, *24*(3), 127–130.

McGregor, A., Lacosta, S., & Roberts, D. C. S. (1993). L-tryptophan decreases the breaking point under a progressive ratio schedule of intravenous cocaine reinforcement in the rat. *Pharmacology Biochemistry and Behavior*, *44*(3), 651–655.

McGuire, P. K., Cope, H., & Fahy, T. A. (1994). Diversity of psychopathology associated with use of 3, 4-methylenedioxymethamphetamine ('Ecstasy'). *The British Journal of Psychiatry*, *165*(3), 391–395.

McKetin, R., Copeland, J., Norberg, M. M., Bruno, R., Hides, L., & Khawar, L. (2014). The effect of the ecstasy "come-down" on the diagnosis of ecstasy dependence. *Drug and Alcohol Dependence*, *139*, 26–32. http://doi.org/10.1016/j.drugalcdep.2014.02.697

Mendrek, A., Blaha, C. D., & Phillips, A. G. (1998). Pre-exposure of rats to amphetamine sensitizes self-administration of this drug under a progressive ratio schedule. *Psychopharmacology*, *135*(4), 416–422. http://doi.org/10.1007/s002130050530

Merck. (1912a). Darstellung von Alkyloxyaryl-, Dialkyloxyarylund Alkylendioxyarylaminopropanen bzw. deren am Stickstoff monoalkylierten Derivaten. Germany: German Imperial Patent Office.

Merck. (1912b). Darstellung von Hydrastininderivaten. Germany: German Imperial Patent Office.

Meyer, M. E., Van Hartesveldt, C., & Potter, T. J. (1993). Locomotor activity following intra-accumbens microinjections of dopamine D1 agonist SK&F 38393 in rats.

Synapse (New York, N.Y.), *13*(4), 310–4. http://doi.org/10.1002/syn.890130403

Millan, M., Newman-Tancredi, A., Quentric, Y., & Cussac, D. (2001). The "selective" dopamine D 1 receptor antagonist, SCH23390, is a potent and high efficacy agonist at cloned human serotonin 2C receptors. *Psychopharmacology*, *156*(1), 58–62. http://doi.org/10.1007/s002130100742

Ministry of Health. Misuse of drugs act 1975. (1975). Retrieved from http://www.legislation.govt.nz/act/public/1975/0116/latest/whole.html

Ministry of Health. (2003). *Drug Use in New Zealand Analysis of the 2003 New Zealand Health Behaviours Survey – Drug Use*. Wellington. Retrieved from http://www.moh.govt.nz/NoteBook/nbbooks.nsf/0/AC0E410721F5E627CC2573430077B889/$file/drug-use-in-new-zealand-analysis-2003-health-behaviours-survey.pdf

Ministry of Health. (2010). *Drug Use in New Zealand. Key Results of the 2007 / 08 New Zealand Alcohol and Drug Use Survey*. Wellington.

Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. G. (1998). Dopamine Receptors: From Structure to Function. *Physiol Rev*, *78*(1), 189–225. Retrieved from http://physrev.physiology.org/content/78/1/189.short

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. http://doi.org/10.1016/0014-2999(87)90441-9

Molloy, A. G., & Waddington, J. L. (1985). Sniffing, rearing and locomotor responses to the D-1 dopamine agonist R-SK&F 38393 and to apomorphine: Differential interactions with the selective D-1 and D-2 antagonists SCH 23390 and metoclopramide. *European Journal of Pharmacology*, *108*(3), 305–308. http://doi.org/10.1016/0014-2999(85)90454-6

Morgan, A. E., Horan, B., Dewey, S. L., & Ashby Jr., C. R. (1997). Repeated administration of 3,4-methylenedioxymethamphetamine augments cocaine's action on dopamine in the nucleus accumbens: a microdialysis study. *Eur J Pharmacol*, *331*(1), R1–3. http://doi.org/10.1016/S0014-2999(97)01035-2

Muller, P., & Seeman, P. (1977). Brain neurotransmitter receptors after long-term haloperidol: Dopamine, acetylcholine, serotonin, !a-noradrenergic and naloxone receptors. *Life Sciences*, *21*(12), 1751–1758.

Munzar, P., Baumann, M. H., Shoaib, M., & Goldberg, S. R. (1999). Effects of dopamine

and serotonin-releasing agents on methamphetamine discrimination and self-administration in rats. *Psychopharmacology*, *141*(3), 287–296. http://doi.org/10.1007/s002130050836

Nader, M. A., & Mach, R. H. (1996). Self-administration of the dopamine D3 agonist 7-OH-DPAT in rhesus monkeys is modified by prior cocaine exposure. *Psychopharmacology*, *125*(1), 13–22. http://doi.org/10.1007/BF02247388

Nagayasu, K., Kitaichi, M., Shirakawa, H., Nakagawa, T., & Kaneko, S. (2010). Sustained Exposure to 3,4-Methylenedioxymethamphetamine Induces the Augmentation of Exocytotic Serotonin Release in Rat Organotypic Raphe Slice Cultures. *Journal of Pharmacological Sciences*, *113*(2), 197–201. http://doi.org/10.1254/jphs.10075SC

Nash, J., & Brodkin, J. (1991). Microdialysis studies on 3,4-methylenedioxymethamphetamine-induced dopamine release: effect of dopamine uptake inhibitors. *J. Pharmacol. Exp. Ther.*, *259*(2), 820–825. Retrieved from http://jpet.aspetjournals.org/content/259/2/820.short

Nichols, D. E., & Glennon, R. A. (1984). Medicinal chemistry and structure-activity relationships of hallucinogens. *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives*. Raven Press: New York.

Norman, A. B., Tabet, M. R., Norman, M. K., & Tsibulsky, V. L. (2011). Using the self-administration of apomorphine and cocaine to measure the pharmacodynamic potencies and pharmacokinetics of competitive dopamine receptor antagonists. *Journal of Neuroscience Methods*, *194*(2), 252–8. http://doi.org/10.1016/j.jneumeth.2010.10.017

O'Connor, E. C., Chapman, K., Butler, P., & Mead, A. N. (2011). The predictive validity of the rat self-administration model for abuse liability. *Neuroscience and Biobehavioral Reviews*, *35*(3), 912–38. http://doi.org/10.1016/j.neubiorev.2010.10.012

O'Hearn, E., Battaglia, G., De Souza, E., Kuhar, M., & Molliver, M. (1988). Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: immunocytochemical evidence for neurotoxicity. *J. Neurosci.*, *8*(8), 2788–2803. Retrieved from http://www.jneurosci.org/content/8/8/2788.short

Oades, R. D., & Halliday, G. M. (1987). Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. *Brain Research Reviews*, *12*(2), 117–165.

http://doi.org/10.1016/0165-0173(87)90011-7

Oakly, A. C., Brox, B. W., Schenk, S., & Ellenbroek, B. A. (2013). A genetic deletion of the serotonin transporter greatly enhances the reinforcing properties of MDMA in rats. *Molecular Psychiatry*, *19*(5), 534–5. http://doi.org/10.1038/mp.2013.75

Overton, D. A. (1987). Applications and limitations of the drug discrimination method for the study of drug abuse. In *Methods of assessing the reinforcing properties of abused drugs* (pp. 291–340). Springer.

Palenicek, T., Votava, M., Bubenikova, V., & Horacek, J. (2005). Increased sensitivity to the acute effects of MDMA ("ecstasy") in female rats. *Physiology & Behavior*, *86*(4), 546–53. http://doi.org/10.1016/j.physbeh.2005.08.043

Parks, K. A., & Kennedy, C. L. (2004). Club drugs: reasons for and consequences of use. *Journal of Psychoactive Drugs*, *36*(3), 295–302. http://doi.org/10.1080/02791072.2004.10400030

Parliament of the United Kingdom. Misuse of Drugs Act 1971 (1971). Retrieved from http://www.legislation.gov.uk/ukpga/1971/38/pdfs/ukpga_19710038_en.pdf

Parrott, A. C. (2001). Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology*, *16*(8), 557–577. http://doi.org/10.1002/hup.351

Parrott, A. C. (2004). Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology*, *173*(3-4), 234–41. http://doi.org/10.1007/s00213-003-1712-7

Parrott, A. C. (2005). Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. *Journal of Psychopharmacology (Oxford, England)*, *19*(1), 71–83. http://doi.org/10.1177/0269881105048900

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. http://doi.org/10.1007/s002130050714

Parrott, A. C., Lees, A., Garnham, N. J., Jones, M., & Wesnes, K. (1998). Cognitive performance in recreational users of MDMA or "ecstasy": evidence for memory deficits. *Journal of Psychopharmacology*, *12*(1), 79–83. http://doi.org/10.1177/026988119801200110

Parrott, A. C., Sisk, E., & Turner, J. J. D. (2000). Psychobiological problems in heavy "ecstasy" (MDMA) polydrug users. *Drug and Alcohol Dependence*, *60*(1), 105–110.

http://doi.org/10.1016/S0376-8716(00)80013-7

Peltier, R., & Schenk, S. (1993). Effects of serotonergic manipulations on cocaine self-administration in rats. *Psychopharmacology*, *110*(4), 390–394. http://doi.org/10.1007/BF02244643

Peroutka, S. J. (1990). Recreational use of MDMA. In *Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA* (pp. 53–62). Springer.

Peroutka, S. J., Newman, H., & Harris, H. (1988). Subjective effects of 3, 4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology*, *1*(4), 273–277.

Pettit, H. O., & Justice, J. B. (1991). Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. *Brain Research*, *539*(1), 94–102. http://doi.org/10.1016/0006-8993(91)90690-W

Pfaus, J. G., Mendelson, S. D., & Phillips, A. G. (1990). A correlational and factor analysis of anticipatory and consummatory measures of sexual behavior in the male rat. *Psychoneuroendocrinology*, *15*(5-6), 329–340. http://doi.org/10.1016/0306-4530(90)90058-H

Pfaus, J. G., & Phillips, A. G. (1991). Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. *Behavioral Neuroscience*, *105*(5), 727.

Phillips, G. D., Robbins, T. W., & Everitt, B. J. (1994). Bilateral intra-accumbens self-administration ofd-amphetamine: Antagonism with intra-accumbens SCH-23390 and sulpiride. *Psychopharmacology*, *114*(3), 477–485. http://doi.org/10.1007/BF02249339

Piazza, P. V., Deminiere, J. M., le Moal, M., & Simon, H. (1990). Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. *Brain Research*, *514*(1), 22–26. http://doi.org/10.1016/0006-8993(90)90431-A

Piazza, P. V., Deminière, J. M., Le Moal, M., & Simon, H. (1989). Factors That Predict Individual Vulnerability to Amphetamine Self-Administration - ProQuest. *Science*, *245*(4925), 1511–1513. Retrieved from http://search.proquest.com/docview/213537533?pq-origsite=gscholar

Piazza, P. V., Maccari, S., Deminiere, J. M., Le Moal, M., Mormede, P., & Simon, H. (1991). Corticosterone levels determine individual vulnerability to amphetamine self-

administration. *Proceedings of the National Academy of Sciences*, *88*(6), 2088–2092. http://doi.org/10.1073/pnas.88.6.2088

Pickens, R., & Harris, W. C. (1968). Self-administration of d-amphetamine by rats. *Psychopharmacologia*, *12*(2), 158–163. http://doi.org/10.1007/BF00401545

Pierce, R. C., & Kalivas, P. W. (1997). A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Research Reviews*, *25*(2), 192–216. http://doi.org/10.1016/S0165-0173(97)00021-0

Pierce, R. C., & Kumaresan, V. (2006). The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience & Biobehavioral Reviews*, *30*(2), 215–238. http://doi.org/10.1016/j.neubiorev.2005.04.016

Pierre, P. J., & Vezina, P. (1997). Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. *Psychopharmacology*, *129*(3), 277–284. http://doi.org/10.1007/s002130050191

Pierre, P. J., & Vezina, P. (1998). D 1 dopamine receptor blockade prevents the facilitation of amphetamine self-administration induced by prior exposure to the drug. *Psychopharmacology*, *138*(2), 159–166. http://doi.org/10.1007/s002130050658

Pope Jr, H. G., Ionescu-Pioggia, M., & Pope, K. W. (2001). Drug use and life style among college undergraduates: a 30-year longitudinal study. *American Journal of Psychiatry*.

Porrino, L. J., Ritz, M. C., Goodman, N. L., Sharpe, L. G., Kuhar, M. J., & Goldberg, S. R. (1989). Differential effects of the pharmacological manipulation of serotonin systems on cocaine and amphetamine self-administration in rats. *Life Sciences*, *45*(17), 1529–35. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2586218

Post, R. M., & Rose, H. (1976). Increasing effects of repetitive cocaine administration in the rat. *Nature*, *260*(5553), 731–732. http://doi.org/10.1038/260731a0

Pritchard, L. M., Van Kempen, T. A., & Zimmerberg, B. (2013). Behavioral effects of repeated handling differ in rats reared in social isolation and environmental enrichment. *Neuroscience Letters*, *536*, 47–51. http://doi.org/10.1016/j.neulet.2012.12.048

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), 100–10.

http://doi.org/10.1007/s00213-004-1937-0

Ramos, M., Goñi-Allo, B., & Aguirre, N. (2005). Administration of SCH 23390 into the medial prefrontal cortex blocks the expression of MDMA-induced behavioral sensitization in rats: an effect mediated by 5-HT2C receptor stimulation and not by D1 receptor blockade. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *30*(12), 2180–91. http://doi.org/10.1038/sj.npp.1300735

Ranaldi, R., Pocock, D., Zereik, R., & Wise, R. A. (1999). Dopamine Fluctuations in the Nucleus Accumbens during Maintenance, Extinction, and Reinstatement of Intravenous D-Amphetamine Self-Administration. *J. Neurosci.*, *19*(10), 4102–4109. Retrieved from http://www.jneurosci.org/content/19/10/4102.short

Ranaldi, R., Wang, Z., & Woolverton, W. L. (2001). Reinforcing effects of D2 dopamine receptor agonists and partial agonists in rhesus monkeys. *Drug and Alcohol Dependence*, *64*(2), 209–217. http://doi.org/10.1016/S0376-8716(01)00124-7

Ratzenboeck, E., Saria, A., Kriechbaum, N., & Zernig, G. (2001). Reinforcing effects of MDMA ("ecstasy") in drug-naive and cocaine-trained rats. *Pharmacology*, *62*(3), 138–44. http://doi.org/56086

Reveron, M. E., Maier, E. Y., & Duvauchelle, C. L. (2006). Experience-dependent changes in temperature and behavioral activity induced by MDMA. *Physiology & Behavior*, *89*(3), 358–63. http://doi.org/10.1016/j.physbeh.2006.06.021

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. *Behav Brain Res*, *207*(2), 500–507. http://doi.org/10.1016/j.bbr.2009.10.038

Ricaurte, G. A., DeLanney, L. E., Irwin, I., & Langston, J. W. (1988). Toxic effects of MDMA on central serotonergic neurons in the primate: importance of route and frequency of drug administration. *Brain Research*, *446*(1), 165–168. http://doi.org/10.1016/0006-8993(88)91309-1

Ricaurte, G. A., Martello, A., Katz, J., & Martello, M. (1992). Lasting effects of (+-)-3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. *J. Pharmacol. Exp. Ther.*, *261*(2), 616–622. Retrieved from http://jpet.aspetjournals.org/content/261/2/616.short

Ricaurte, G. A., McCann, U. D., Szabo, Z., & Scheffel, U. (2000). Toxicodynamics and

long-term toxicity of the recreational drug, 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). *Toxicology Letters*, *112-113*, 143–146. http://doi.org/10.1016/S0378-4274(99)00216-7

Richardson, N. R., & Roberts, D. C. S. (1991). Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. *Life Sciences*, *49*(11), 833–840.

Risbrough, V. B., Masten, V. L., Caldwell, S., Paulus, M. P., Low, M. J., & Geyer, M. A. (2006). Differential contributions of dopamine D1, D2, and D3 receptors to MDMA-induced effects on locomotor behavior patterns in mice. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *31*(11), 2349–58. http://doi.org/10.1038/sj.npp.1301161

Risner, M. E., & Jones, B. E. (1975). Self-administration of CNS stimulants by dog. *Psychopharmacologia*, *43*(3), 207–213. http://doi.org/10.1007/BF00429252

Risner, M. E., & Jones, B. E. (1976). Role of noradrenergic and dopaminergic processes in amphetamine self-administration. *Pharmacology Biochemistry and Behavior*, *5*(4), 477–482. http://doi.org/10.1016/0091-3057(76)90113-1

Roberts, D. C. S., Corcoran, M. E., & Fibiger, H. C. (1977). On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacology Biochemistry and Behavior*, *6*(6), 615–620. http://doi.org/10.1016/0091-3057(77)90084-3

Roberts, D. C. S., & Koob, G. F. (1982). Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. *Pharmacology Biochemistry and Behavior*, *17*(5), 901–904. http://doi.org/10.1016/0091-3057(82)90469-5

Roberts, D. C. S., Koob, G. F., Klonoff, P., & Fibiger, H. C. (1980). Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacology Biochemistry and Behavior*, *12*(5), 781–787. http://doi.org/10.1016/0091-3057(80)90166-5

Roberts, D. C. S., Phelan, R., Hodges, L. M., Hodges, M. M., Bennett, B., Childers, S., & Davies, H. (1999). Self-administration of cocaine analogs by rats. *Psychopharmacology*, *144*(4), 389–397. http://doi.org/10.1007/s002130051022

Robinson, T. E. (1984). Behavioral sensitization: Characterization of enduring changes in rotational behavior produced by intermittent injections of amphetamine in male and

female rats. *Psychopharmacology*, *84*(4), 466–475. http://doi.org/10.1007/BF00431451

Robinson, T. E., & Becker, J. B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. *Brain Research Reviews*, *11*(2), 157–198. http://doi.org/10.1016/0165-0173(86)90002-0

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*, *18*(3), 247–291. http://doi.org/10.1016/0165-0173(93)90013-P

Rodd-Henricks, Z. A., Bell, R. L., Kuc, K. A., Murphy, J. M., McBride, W. J., Lumeng, L., & Li, T.-K. (2002). Effects of Ethanol Exposure on Subsequent Acquisition and Extinction of Ethanol Self-Administration and Expression of Alcohol-Seeking Behavior in Adult Alcohol-Preferring (P) Rats: I. Periadolescent Exposure. *Alcoholism: Clinical and Experimental Research*, *26*(11), 1632–1641. http://doi.org/10.1111/j.1530-0277.2002.tb02465.x

Roiser, J. P., Rogers, R. D., Cook, L. J., & Sahakian, B. J. (2006). The effect of polymorphism at the serotonin transporter gene on decision-making, memory and executive function in ecstasy users and controls. *Psychopharmacology*, *188*(2), 213–27. http://doi.org/10.1007/s00213-006-0495-z

Rudnick, G., & Wall, S. C. (1992). The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. *Proceedings of the National Academy of Sciences*, *89*(5), 1817–1821. http://doi.org/10.1073/pnas.89.5.1817

Sabol, K. E., & Seiden, L. S. (1998). Reserpine attenuates d-amphetamine and MDMA-induced transmitter release in vivo: a consideration of dose, core temperature and dopamine synthesis. *Brain Research*, *806*(1), 69–78. http://doi.org/10.1016/S0006-8993(98)00720-3

Sadananda, M., Natusch, C., Karrenbauer, B., & Schwarting, R. K. W. (2012). 50-kHz calls in rats: effects of MDMA and the 5-HT(1A) receptor agonist 8-OH-DPAT. *Pharmacology, Biochemistry, and Behavior*, *101*(2), 258–64. http://doi.org/10.1016/j.pbb.2012.01.012

Salmi, P., & Ahlenius, S. (2000). Sedative effects of the dopamine D1 receptor agonist A 68930 on rat open-field behavior. *Neuroreport*, *11*(6), 1269–1272.

Scanzello, C., Hatzidimitriou, G., Martello, A., Katz, J., & Ricaurte, G. A. (1993). Serotonergic recovery after (+/-)3,4-(methylenedioxy) methamphetamine injury: observations in rats. *J. Pharmacol. Exp. Ther.*, *264*(3), 1484–1491. Retrieved from http://jpet.aspetjournals.org/content/264/3/1484.short

Schenk, S. (2009). MDMA self-administration in laboratory animals: a summary of the literature and proposal for future research. *Neuropsychobiology*, *60*(3-4), 130–6. http://doi.org/10.1159/000253549

Schenk, S. (2011). MDMA ("ecstasy") abuse as an example of dopamine neuroplasticity. *Neuroscience and Biobehavioral Reviews*, *35*(5), 1203–18. http://doi.org/10.1016/j.neubiorev.2010.12.010

Schenk, S., & Bradbury, S. (2015). Persistent sensitisation to the locomotor activating effects of MDMA following MDMA self-administration in rats. *Pharmacology, Biochemistry, and Behavior*, *132*, 103–107. http://doi.org/10.1016/j.pbb.2015.03.001

Schenk, S., Colussi-Mas, J., Do, J., & Bird, J. (2012). Profile of MDMA self-administration from a large cohort of rats: MDMA develops a profile of dependence with extended testing. *J Drug Alcohol Res*, *1*, 1–6.

Schenk, S., Gittings, D., & Colussi-Mas, J. (2011). Dopaminergic mechanisms of reinstatement of MDMA-seeking behaviour in rats. *British Journal of Pharmacology*, *162*(8), 1770–80. http://doi.org/10.1111/j.1476-5381.2010.01193.x

Schenk, S., Gittings, D., Johnstone, M., & Daniela, E. (2003). Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats. *Psychopharmacology*, *169*(1), 21–7. http://doi.org/10.1007/s00213-003-1407-0

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. http://doi.org/10.1016/j.drugalcdep.2008.03.014

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. *The European Journal of Neuroscience*, *26*(11), 3229–36. http://doi.org/10.1111/j.1460-9568.2007.05932.x

Schenk, S., Valadez, A., McNamara, C., House, D. T., Higley, D., Bankson, M. G., … Horger, B. A. (1993). Development and expression of sensitization to cocaine's reinforcing properties: role of NMDA receptors. *Psychopharmacology*, *111*(3), 332–

338. http://doi.org/10.1007/BF02244949

Schifano, F., Oyefeso, A., Corkery, J., Cobain, K., Jambert-Gray, R., Martinotti, G., & Ghodse, A. H. (2003). Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996-2002. *Human Psychopharmacology*, *18*(7), 519–24. http://doi.org/10.1002/hup.528

Schmidt, C. (1987). Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J. Pharmacol. Exp. Ther.*, *240*(1), 1–7. Retrieved from http://jpet.aspetjournals.org/content/240/1/1.short

Schott, B. H., Minuzzi, L., Krebs, R. M., Elmenhorst, D., Lang, M., Winz, O. H., … Bauer, A. (2008). Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*(52), 14311–9. http://doi.org/10.1523/JNEUROSCI.2058-08.2008

Schuldiner, S., Steiner-Mordoch, S., Yelin, R., Wall, S., & Rudnick, G. (1993). Amphetamine derivatives interact with both plasma membrane and secretory vesicle biogenic amine transporters. *Mol. Pharmacol.*, *44*(6), 1227–1231. Retrieved from http://molpharm.aspetjournals.org/content/44/6/1227.short

Schultz, W., Apicella, P., & Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.*, *13*(3), 900–913. Retrieved from http://www.jneurosci.org/content/13/3/900.short

Schuster, C. R., & Thompson, T. (1969). Self administration of and behavioral dependence on drugs. *Annual Review of Pharmacology*, *9*(1), 483–502.

Schuster, P., Lieb, R., Lamertz, C., & Wittchen, H.-U. (1998). Is the Use of Ecstasy and Hallucinogens Increasing? *European Addiction Research*, *4*(1-2), 75–82. http://doi.org/10.1159/000018925

Scorza, M. C., Carrau, C., Silveira, R., Zapata-Torres, G., Cassels, B. K., & Reyes-Parada, M. (1997). Monoamine Oxidase Inhibitory Properties of Some Methoxylated and Alkylthio Amphetamine Derivatives. *Biochemical Pharmacology*, *54*(12), 1361–1369. http://doi.org/10.1016/S0006-2952(97)00405-X

Screaton, G. R., Cairns, H. S., Sarner, M., Singer, M., Thrasher, A., & Cohen, S. L. (1992). Hyperpyrexia and rhabdomyolysis after MDMA (“ ecstasy”) abuse. *The Lancet*, *339*(8794), 677–678.

Seeman, P., McCormick, P. N., & Kapur, S. (2007). Increased dopamine D2(High) receptors in amphetamine-sensitized rats, measured by the agonist [(3)H](+)PHNO. *Synapse (New York, N.Y.)*, *61*(5), 263–7. http://doi.org/10.1002/syn.20367

Seevers, M. H., & Tatum, A. L. (1931). CHRONIC EXPERIMENTAL BARBITAL POISONING. *J. Pharmacol. Exp. Ther.*, *42*(2), 217–231. Retrieved from http://jpet.aspetjournals.org/content/42/2/217.short

Self, D. W., Belluzzi, J. D., Kossuth, S., & Stein, L. (1996). Self-administration of the D1 agonist SKF 82958 is mediated by D1, not D2, receptors. *Psychopharmacology*, *123*(4), 303–306. http://doi.org/10.1007/BF02246638

Self, D. W., & Stein, L. (1992). The D1 agonists SKF 82958 and SKF 77434 are self-administered by rats. *Brain Research*, *582*(2), 349–352. http://doi.org/10.1016/0006-8993(92)90155-3

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. http://doi.org/10.1192/bjp.175.1.63

Series, H., Boeles, S., Dorkins, E., & Peveler, R. (1994). Psychiatric complications of "Ecstasy" use. *Journal of Psychopharmacology (Oxford, England)*, *8*(1), 60–1. http://doi.org/10.1177/026988119400800110

Shaham, Y., Shalev, U., Lu, L., De Wit, H., & Stewart, J. (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology*, *168*(1-2), 3–20. http://doi.org/10.1007/s00213-002-1224-x

Shankaran, M., & Gudelsky, G. A. (1999). A neurotoxic regimen of MDMA suppresses behavioral, thermal and neurochemical responses to subsequent MDMA administration. *Psychopharmacology*, *147*(1), 66–72. http://doi.org/10.1007/s002130051143

Shulgin, A. T. (2012). The background and chemistry of MDMA. *Journal of Psychoactive Drugs*, *18*(4), 291–304. http://doi.org/10.1080/02791072.1986.10472361

Shulgin, A. T., & Nichols, D. E. (1978). Characterization of three new psychotomimetics. In *The Pharmacology of Hallucinogens.* (pp. 74–83). New York: Pergamon. Retrieved from http://www.researchgate.net/publication/268342762_CHARACTERIZATION_OF_THREE_NEW_PSYCHOTOMIMETICS

Singer, G., Wallace, M., & Hall, R. (1982). Effects of dopaminergic nucleus accumbens lesions on the acquisition of schedule induced self injection of nicotine in the rat. *Pharmacology Biochemistry and Behavior*, *17*(3), 579–581. http://doi.org/10.1016/0091-3057(82)90321-5

Slack, A., Nana, G., Webster, M., Stokes, F., & Wu, J. (2009). *Report to: Ministry of Health and ACC. COSTS OF HARMFUL ALCOHOL AND OTHER DRUG USE*. Retrieved from http://www.justice.govt.nz/justice-sector/drivers-of-crime/documents/BERL_-July_2009-_Costs_of_Harmful_Alcohol_and_Other_Drug_Use-1.pdf

Smith, J. E., Dianna, S. L., Smith, D. G., Leccese, A. P., & Lyness, W. H. (1986). Dietary tryptophan supplements attenuate amphetamine self-administration in the rat. *Pharmacology Biochemistry and Behavior*, *25*(4), 849–855.

Smith, J. E., Shultz, K., Co, C., Goeders, N. E., & Dworkin, S. I. (1987). Effects of 5, 7-dihydroxytryptamine lesions of the nucleus accumbens on rat inravenous morphine self-administration. *Pharmacology Biochemistry and Behavior*, *26*(3), 607–612.

Solowij, N., Hall, W., & Lee, N. (1992). Recreational MDMA use in Sydney: a profile of "Ecstasy" users and their experiences with the drug. *Addiction*, *87*(8), 1161–1172. http://doi.org/10.1111/j.1360-0443.1992.tb02003.x

Spanos, L. J., & Yamamoto, B. K. (1989). Acute and subchronic effects of methylenedioxymethamphetamine [(±)MDMA] on locomotion and serotonin syndrome behavior in the rat. *Pharmacology Biochemistry and Behavior*, *32*(4), 835–840. http://doi.org/10.1016/0091-3057(89)90044-0

Steinpreis, R. E., & Salamone, J. D. (1993). The role of nucleus accumbens dopamine in the neurochemical and behavioral effects of phencyclidine: a microdialysis and behavioral study. *Brain Research*, *612*(1-2), 263–270. http://doi.org/10.1016/0006-8993(93)91671-E

Stewart, J., & Badiani, A. (1993). Tolerance and sensitization to the behavioral effects of drugs. *Behavioural Pharmacology*, *4*(4), 289–312.

Stone, D. M., Merchant, K. M., Hanson, G. R., & Gibb, J. W. (1987). Immediate and long-term effects of 3,4-methylenedioxymethamphetamine on serotonin pathways in brain of rat. *Neuropharmacology*, *26*(12), 1677–1683. http://doi.org/10.1016/0028-3908(87)90117-1

Strote, J., Lee, J. E., & Wechsler, H. (2002). Increasing MDMA use among college

students: results of a national survey. *Journal of Adolescent Health*, *30*(1), 64–72. http://doi.org/10.1016/S1054-139X(01)00315-9

Sulzer, D., & Rayport, S. (1990). Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: A mechanism of action. *Neuron*, *5*(6), 797–808. http://doi.org/10.1016/0896-6273(90)90339-H

Tanabe, L. M., Suto, N., Creekmore, E., Steinmiller, C. L., & Vezina, P. (2004). Blockade of D2 dopamine receptors in the VTA induces a long-lasting enhancement of the locomotor activating effects of amphetamine. *Behavioural Pharmacology*, *15*(5-6), 387–95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15343065

Tancer, M., & Johanson, C.-E. (2003). Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. *Drug and Alcohol Dependence*, *72*(1), 33–44. http://doi.org/10.1016/S0376-8716(03)00172-8

Tegner, M. (1977). Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain. *Science, 196*, 326–328.

Tessel, R. E., & Woods, J. H. (1975). Fenfluramine and N-ethyl amphetamine: Comparison of the reinforcing and rate-decreasing actions in the rhesus monkey. *Psychopharmacologia*, *43*(3), 239–244. http://doi.org/10.1007/BF00429257

Thomasius, R., Petersen, K., Buchert, R., Andresen, B., Zapletalova, P., Wartberg, L., … Schmoldt, A. (2003). Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. *Psychopharmacology*, *167*(1), 85–96. http://doi.org/10.1007/s00213-002-1383-9

Thomasius, R., Zapletalova, P., Petersen, K., Buchert, R., Andresen, B., Wartberg, L., … Schmoldt, A. (2006). Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *Journal of Psychopharmacology (Oxford, England)*, *20*(2), 211–25. http://doi.org/10.1177/0269881106059486

Thompson, M. R., Callaghan, P. D., Hunt, G. E., Cornish, J. L., & McGregor, I. S. (2007). A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). *Neuroscience*, *146*(2), 509–14. http://doi.org/10.1016/j.neuroscience.2007.02.032

Thompson, T., & Schuster, C. R. (1964). Morphine self-administration, food-reinforced, and avoidance behaviors in rhesus monkeys. *Psychopharmacologia*, *5*(2), 87–94. http://doi.org/10.1007/BF00413045

Topp, L., Hall, W., & Hando, J. (1997). *Is there a dependence syndrome for ecstasy?* NDARC.

Topp, L., Hando, J., Dillon, P., Roche, A., & Solowij, N. (1999). Ecstasy use in Australia: patterns of use and associated harm. *Drug and Alcohol Dependence*, *55*(1-2), 105–115. http://doi.org/10.1016/S0376-8716(99)00002-2

Torre, R., Farre, M., Roset, P. N., López, C. H., Mas, M., Ortuño, J., … Camí, J. (2006). Pharmacology of MDMA in Humans. *Annals of the New York Academy of Sciences*, *914*(1), 225–237. http://doi.org/10.1111/j.1749-6632.2000.tb05199.x

Trigo, J. M., Panayi, F., Soria, G., Maldonado, R., & Robledo, P. (2006). A reliable model of intravenous MDMA self-administration in naïve mice. *Psychopharmacology*, *184*(2), 212–20. http://doi.org/10.1007/s00213-005-0229-7

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. http://doi.org/10.1111/j.1369-1600.2007.00070.x

Ujike, H., Akiyama, K., & Otsuki, S. (1990). D-2 but not D-1 dopamine agonists produce augmented behavioral response in rats after subchronic treatment with methamphetamine or cocaine. *Psychopharmacology*, *102*(4), 459–464. http://doi.org/10.1007/BF02247125

Ungerstedt, U. (1979). Central dopamine mechanisms and unconditioned behaviour. *The Neurobiology of Dopamine*, 577–596.

United Nations Office on Drugs and Crime [UNODC]. (2015). *World Drug Report 2015*. London. Retrieved from http://www.unodc.org/wdr2015/

Valadez, A., & Schenk, S. (1994). Persistence of the ability of amphetamine preexposure to facilitate acquisition of cocaine self-administration. *Pharmacology Biochemistry and Behavior*, *47*(1), 203–205. http://doi.org/10.1016/0091-3057(94)90132-5

Vanderschuren, L. J. M. J., & Kalivas, P. W. (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology*, *151*(2-3), 99–120. http://doi.org/10.1007/s002130000493

Vanderschuren, L. J. M. J., Schmidt, E. D., De Vries, T. J., Van Moorsel, C. A. P., Tilders, F. J. H., & Schoffelmeer, A. N. M. (1999). A Single Exposure to Amphetamine Is Sufficient to Induce Long-Term Behavioral, Neuroendocrine, and Neurochemical Sensitization in Rats. *J. Neurosci.*, *19*(21), 9579–9586. Retrieved from

http://www.jneurosci.org/content/19/21/9579.full

Vanderschuren, L. J. M. J., Schoffelmeer, A. N. M., Mulder, A. H., & De Vries, T. J. (1999). Dopaminergic mechanisms mediating the long-term expression of locomotor sensitization following pre-exposure to morphine or amphetamine. *Psychopharmacology*, *143*(3), 244–253. http://doi.org/10.1007/s002130050943

Vanover, K. E., Nader, M. A., & Woolverton, W. L. (1992). Evaluation of the discriminative stimulus and reinforcing effects of sertraline in rhesus monkeys. *Pharmacology, Biochemistry, and Behavior*, *41*(4), 789–93. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1594647

Vazquez-DeRose, J., Stauber, G., Khroyan, T. V, Xie, X. S., Zaveri, N. T., & Toll, L. (2013). Retrodialysis of N/OFQ into the nucleus accumbens shell blocks cocaine-induced increases in extracellular dopamine and locomotor activity. *European Journal of Pharmacology*, *699*(1-3), 200–6. http://doi.org/10.1016/j.ejphar.2012.11.050

Verkes, R. J., Gijsman, H. J., Pieters, M. S. M., 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. http://doi.org/10.1007/s002130000563

Vezina, P. (1993). Amphetamine injected into the ventral tegmental area sensitizes the nucleus accumbens dopaminergic response to systemic amphetamine: an in vivo microdialysis study in the rat. *Brain Research*, *605*(2), 332–337. http://doi.org/10.1016/0006-8993(93)91761-G

Vezina, P. (1996). D1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. *J. Neurosci.*, *16*(7), 2411–2420. Retrieved from http://www.jneurosci.org/content/16/7/2411.short

Vezina, P. (2004). Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. *Neuroscience and Biobehavioral Reviews*, *27*(8), 827–39. http://doi.org/10.1016/j.neubiorev.2003.11.001

Vezina, P., Lorrain, D. S., Arnold, G. M., Austin, J. D., & Suto, N. (2002). Sensitization of Midbrain Dopamine Neuron Reactivity Promotes the Pursuit of Amphetamine. *J. Neurosci.*, *22*(11), 4654–4662. Retrieved from http://www.jneurosci.org/content/22/11/4654.full

Vezina, P., & Stewart, J. (1989). The effect of dopamine receptor blockade on the

development of sensitization to the locomotor activating effects of amphetamine and morphine. *Brain Research*, *499*(1), 108–120. http://doi.org/10.1016/0006-8993(89)91140-2

Vollenweider, F. X., Gamma, A., Liechti, M., & Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *19*(4), 241–51. http://doi.org/10.1016/S0893-133X(98)00013-X

von Sydow, K., Lieb, R., Pfister, H., Höfler, M., & Wittchen, H.-U. (2002). Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults—a transient phenomenon? Results from a longitudinal community study. *Drug and Alcohol Dependence*, *66*(2), 147–159. http://doi.org/10.1016/S0376-8716(01)00195-8

Wang, Y., Joharchi, N., Fletcher, P. J., Sellers, E. M., & Higgins, G. A. (1995). Further studies to examine the nature of dexfenfluramine-induced suppression of heroin self-administration. *Psychopharmacology*, *120*(2), 134–141. http://doi.org/10.1007/BF02246185

Wang, Z., & Woolverton, W. L. (2007). Estimating the relative reinforcing strength of (+/-)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine. *Psychopharmacology*, *189*(4), 483–8. http://doi.org/10.1007/s00213-006-0599-5

Wee, S., Anderson, K. G., Baumann, M. H., Rothman, R. B., Blough, B. E., & Woolverton, W. L. (2005). Relationship between the serotonergic activity and reinforcing effects of a series of amphetamine analogs. *The Journal of Pharmacology and Experimental Therapeutics*, *313*(2), 848–54. http://doi.org/10.1124/jpet.104.080101

Wee, S., & Woolverton, W. L. (2006). Self-administration of mixtures of fenfluramine and amphetamine by rhesus monkeys. *Pharmacology, Biochemistry, and Behavior*, *84*(2), 337–43. http://doi.org/10.1016/j.pbb.2006.05.022

Weed, M., & Woolverton, W. L. (1995). The reinforcing effects of dopamine D1 receptor agonists in rhesus monkeys. *J. Pharmacol. Exp. Ther.*, *275*(3), 1367–1374. Retrieved from http://jpet.aspetjournals.org/content/275/3/1367.short

Weeks, J. R. (1962). Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. *Science*, *138*(3537), 143–144.

Weeks, J. R., & Collins, R. J. (1964). Factors affecting voluntary morphine intake in self-maintained addicted rats. *Psychopharmacologia*, *6*(4), 267–279. http://doi.org/10.1007/BF00413156

Weir, E. (2000). Raves: a review of the culture, the drugs and the prevention of harm. *Can. Med. Assoc. J.*, *162*(13), 1843–1848. Retrieved from http://www.cmaj.ca/content/162/13/1843.short

White, F. J., Joshi, A., Koeltzow, T. E., & Hu, X. T. (1998). Dopamine receptor antagonists fail to prevent induction of cocaine sensitization. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *18*(1), 26–40. http://doi.org/10.1016/S0893-133X(97)00093-6

Wilkins, C., Bhatta, K., Pledger, M., & Casswell, S. (2003). Ecstasy use in New Zealand: findings from the 1998 and 2001 National Drug Surveys. *New Zealand Medical Journal*, *116*(1171), 1–10.

Wilkins, C., Jawalkar, P., Moewaka Barnes, H., Parker, K., & Asiasiga, L. (2014). *New Zealand Arrestee Drug Use Monitoring*.

Wilkins, C., Prasad, J., Wong, K., & Rychert, M. (2014). *Recent Trends in Illegal Drug Use in New Zealand, 2006-2013*. Retrieved from http://www.massey.ac.nz/massey/fms/Colleges/College of Humanities and Social Sciences/Shore/reports/IDMS 2013 report.pdf?6908B6F2215DE8669735157C0938DC08

Williamson, S. (1997). Adverse effects of stimulant drugs in a community sample of drug users. *Drug and Alcohol Dependence*, *44*(2-3), 87–94. http://doi.org/10.1016/S0376-8716(96)01324-5

Wilson, M. A., Ricaurte, G. A., & Molliver, M. E. (1989). Distinct morphologic classes of serotonergic axons in primates exhibit differential vulnerability to the psychotropic drug 3,4-methylenedioxymethamphetamine. *Neuroscience*, *28*(1), 121–137. http://doi.org/10.1016/0306-4522(89)90237-6

Winstock, A. R. (2015). Global drug survey 2015. Retrieved July 10, 2015, from http://www.globaldrugsurvey.com/the-global-drug-survey-2015-findings/

Winstock, A. R., Griffiths, P., & Stewart, D. (2001). Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. *Drug and Alcohol Dependence*, *64*(1), 9–17. http://doi.org/10.1016/S0376-

8716(00)00215-5

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, *5*(6), 483–494.

Wise, R. A., Leeb, K., Pocock, D., Newton, P., Burnette, B., & Justice, J. B. (1995). Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology*, *120*(1), 10–20. http://doi.org/10.1007/BF02246140

Woolverton, W. L., Goldberg, L., & Ginos, J. (1984). Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *J. Pharmacol. Exp. Ther.*, *230*(3), 678–683. Retrieved from http://jpet.aspetjournals.org/content/230/3/678.short

Yen, C.-F., & Hsu, S.-Y. (2007). Symptoms of ecstasy dependence and correlation with psychopathology in Taiwanese adolescents. *The Journal of Nervous and Mental Disease*, *195*(10), 866–869.

Yokel, R. A., & Wise, R. A. (1976). Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology*, *48*(3), 311–318. http://doi.org/10.1007/BF00496868

Yokel, R. A., & Wise, R. A. (1978). Amphetamine-type reinforcement by dopaminergic agonists in the rat. *Psychopharmacology*, *58*(3), 289–296. http://doi.org/10.1007/BF00427393

Zhao, W., & Becker, J. B. (2010). Sensitization enhances acquisition of cocaine self-administration in female rats: estradiol further enhances cocaine intake after acquisition. *Hormones and Behavior*, *58*(1), 8–12. http://doi.org/10.1016/j.yhbeh.2009.09.005

Appendix A

Experiment 1: statistical results.

Table A1.
3 (eticlopride dose: 0.0, 0.05, 0.3) × 5 (session: 1-5) mixed measures ANOVA

Basal total locomotor activity		
Interaction:	Etic dose × session	$F(8, 92) = 2.78$, $p = .009$, $\eta_p^2 = .194$
Simple main effect:	Etic dose on session 1[1]	$p = .099$
	Etic dose on session 2[1]	$p = .057$
	Etic dose on session 3[1]	$p = .060$
	Etic dose on session 4[1]	$p = .106$
	Etic dose on session 5[1]	$p = .415$
Basal centre locomotor activity		
Interaction:	Etic dose × session	$F(8, 92) = 3.47$, $p = .002$, $\eta_p^2 = .232$
Simple main effect:	Etic dose on session 1[1]	$p = .436$
	Etic dose on session 2[1]	$p = .297$
	Etic dose on session 3[1]	$p = .154$
	Etic dose on session 4[1]	$p = .091$
	Etic dose on session 5[1]	$p = .071$
Basal peripheral locomotor activity		
Interaction:	Etic dose × session	$F(8, 92) = 2.20$, $p = .035$, $\eta_p^2 = .160$
Simple main effect:	Etic dose on session 1[1]	$p = .061$
	Etic dose on session 2[1]	$p = .052$
	Etic dose on session 3[1]	$p = .060$
	Etic dose on session 4[1]	$p = .181$
	Etic dose on session 5[1]	$p = .744$

[1] Level of significance accepted at $p < .01$.

Table A2.
2 (MDMA dose: 0.0, 10.0) × 5 (session: 1-5) mixed measures ANOVA

Total locomotor activity		
Interaction:	MDMA dose × session	$p = .205$
Main effect:	MDMA dose	$F(1, 19) = 149.80$, $p < .001$, $\eta_p^2 = .887$
	Session	$p = .205$
Centre locomotor activity		
Interaction:	MDMA dose × session	$F(2.32, 44.07) = 5.44$, $p = .006$, $\eta_p^2 = .223$
Simple main effect:	MDMA dose on session 1[1]	$F(1, 19) = 20.88$, $p < .001$, $\eta_p^2 = .524$
	MDMA dose on session 2[1]	$F(1, 19) = 18.32$, $p < .001$, $\eta_p^2 = .491$
	MDMA dose on session 3[1]	$F(1, 19) = 44.60$, $p < .001$, $\eta_p^2 = .701$
	MDMA dose on session 4[1]	$F(1, 19) = 28.95$, $p < .001$, $\eta_p^2 = .604$
	MDMA dose on session 5[1]	$F(1, 19) = 90.19$, $p < .001$, $\eta_p^2 = .826$
	Session on MDMA 10.0	$F(4, 40) = 5.82$, $p = .001$, $\eta_p^2 = .368$
Simple comparisons[2]:	Session 2 vs 3	$p = .026$
	Session 2 vs 5	$p < .001$
Peripheral locomotor activity		
Interaction:	MDMA dose × session	$p = .476$
Main effect:	MDMA dose	$F(1, 19) = 117.92$, $p < .001$, $\eta_p^2 = .861$
	Session	$p = .355$

[1] Level of significance accepted at $p < .01$.
[2] All other comparisons were not significant.

Table A3.
3 (eticlopride dose: 0.0, 0.05, 0.3) × 5 (session: 1-5) mixed measures ANOVA

MDMA-produced total locomotor activity		
Interaction:	Etic dose × session	$p = .200$
Main effect:	Etic dose	$F(2, 23) = 56.29$, $p < .001$, $\eta_p^2 = .830$
	Session	$p = .112$
Tukey HSD:	Etic 0.0 vs 0.05	$p < .001$
	Etic 0.0 vs 0.03	$p < .001$
	Etic 0.05 vs 0.3	$p = .677$
MDMA-produced centre locomotor activity		
Interaction:	Etic dose × session	$F(6.05, 69.62) = 2.98$, $p = .012$, $\eta_p^2 = .206$
Simple main effect:	Etic dose on session 1[1]	$F(2, 23) = 9.91$, $p = .001$, $\eta_p^2 = .463$
	Etic dose on session 2[1]	$p = .610$
	Etic dose on session 3[1]	$F(2, 23) = 11.10$, $p < .001$, $\eta_p^2 = .491$
	Etic dose on session 4[1]	$F(2, 23) = 6.23$, $p = .007$, $\eta_p^2 = .351$
	Etic dose on session 5[1]	$F(2, 23) = 12.82$, $p < .001$, $\eta_p^2 = .368$
Tukey HSD (session 1):	Etic 0.0 vs 0.05	$p = .013$
	Etic 0.0 vs 0.03	$p = .001$
	Etic 0.05 vs 0.3	$p = .680$
Tukey HSD (session 3):	Etic 0.0 vs 0.05	$p = .164$
	Etic 0.0 vs 0.03	$p < .001$
	Etic 0.05 vs 0.3	$p = .054$
Tukey HSD (session 4):	Etic 0.0 vs 0.05	$p = .073$
	Etic 0.0 vs 0.03	$p = .007$
	Etic 0.05 vs 0.3	$p = .667$
Tukey HSD (session 5):	Etic 0.0 vs 0.05	$p = .141$
	Etic 0.0 vs 0.03	$p < .001$
	Etic 0.05 vs 0.3	$p = .033$
MDMA-produced peripheral locomotor activity		
Interaction:	Etic dose × session	$p = .377$
Main effect:	Etic dose	$F(2, 23) = 48.39$, $p < .001$, $\eta_p^2 = .808$
	Session	$p = .093$
Tukey HSD:	Etic 0.0 vs 0.05	$p < .001$
	Etic 0.0 vs 0.03	$p < .001$
	Etic 0.05 vs 0.3	$p = .892$

[1] Level of significance accepted at $p < .01$.

Table A4
2 (box zone: centre, periphery) × 5 (session: 1-5) repeated measures ANOVA

Percent change in MDMA-produced total locomotor activity		
Interaction:	Box zone × session	$F(4, 40) = 5.24$, $p = .002$, $\eta_p^2 = .344$
Simple main effect:	Box zone on session 1[1]	$p = .966$
	Box zone on session 2[1]	$F(1, 10) = 17.96$, $p = .002$, $\eta_p^2 = .642$
	Box zone on session 3[1]	$p = .400$
	Box zone on session 4[1]	$p = .605$
	Box zone on session 5[1]	$p = .076$
	Session on centre[2]	$F(4, 40) = 5.84$, $p = .001$, $\eta_p^2 = .369$
	Session on periphery[2]	$p = .386$
Simple comparisons (centre)[3]:	Session 2 vs 3	$p = .026$
	Session 2 vs 5	$p < .001$

[1] Level of significance accepted at $p < .01$.
[2] Level of significance accepted at $p < .025$.
[3] All other comparisons were not significant.

Table A5
3 (eticlopride dose: 0.0, 0.05, 0.3) × 2 (MDMA dose: 0.0, 10.0) ANOVA

Total locomotor activity		
Interaction:	Etic dose × MDMA dose	$F(2, 44) = 10.17$, $p < .001$, $\eta_p^2 = .316$
Simple main effect:	MDMA dose on etic 0.0	$F(1, 44) = 28.19$, $p < .001$, $\eta_p^2 = .391$
	Etic dose on MDMA 10.0	$F(2, 44) = 8.84$, $p = .001$, $\eta_p^2 = .287$
Simple comparisons:	Etic 0.0 vs 0.05	$p = .022$
	Etic 0.0 vs 0.3	$p = .001$
	Etic 0.05 vs 0.3	$p = .999$
Centre locomotor activity		
Interaction:	Etic dose × MDMA dose	$F(2, 44) = 4.37$, $p = .019$, $\eta_p^2 = .166$
Simple main effect:	MDMA dose on etic 0.0	$F(1, 44) = 35.28$, $p < .001$, $\eta_p^2 = .226$
	Etic dose on MDMA 10.0	$F(2, 44) = 8.16$, $p = .001$, $\eta_p^2 = .271$
Simple comparisons:	Etic 0.0 vs 0.05	$p = .442$
	Etic 0.0 vs 0.3	$p = .001$
	Etic 0.05 vs 0.3	$p = .089$
Peripheral locomotor activity		
Interaction:	Etic dose × MDMA dose	$F(2, 44) = 8.57$, $p = .001$, $\eta_p^2 = .280$
Simple main effect:	MDMA dose on etic 0.0	$F(1, 44) = 16.42$, $p < .001$, $\eta_p^2 = .272$
	Etic dose on MDMA 10.0	$F(2, 44) = 6.14$, $p = .004$, $\eta_p^2 = .218$
Simple comparisons:	Etic 0.0 vs 0.05	$p = .034$
	Etic 0.0 vs 0.3	$p = .008$
	Etic 0.05 vs 0.3	$p = .999$
Basal locomotor activity		
Interaction:	Etic dose × MDMA dose	$p = .056$
Main effect:	Etic dose	$p = .188$
	MDMA dose	$p = .465$

Appendix B
Experiment 2: statistical results.

Table B1.
2 (eticlopride dose: 0.0, 0.3) × 5 (session: 1-5) mixed measures ANOVA

Basal total locomotor activity		
Interaction:	Etic dose × session	$p = .050$
Main effect:	Etic dose	$F(1, 22) = 16.55$, $p = .001$, $\eta_p^2 = .429$
	Session	$p = .202$
Basal centre locomotor activity		
Interaction:	Etic dose × session	$F(2.75, 60.47) = 3.23$, $p = .032$, $\eta_p^2 = .128$
Simple main effect:	Etic dose on session 1[1]	$p = .090$
	Etic dose on session 2[1]	$p = .026$
	Etic dose on session 3[1]	$F(1, 22) = 11.12$, $p = .003$, $\eta_p^2 = .336$
	Etic dose on session 4[1]	$p = .224$
	Etic dose on session 5[1]	$p = .083$
Basal peripheral locomotor activity		
Interaction:	Etic dose × session	$p = .175$
Main effect:	Etic dose	$F(1, 21) = 15.57$, $p = .001$, $\eta_p^2 = .414$
	Session	$p = .358$

[1] Level of significance accepted at $p < .01$.

Table B2.
2 (MDMA dose: 0.0, 10.0) × 5 (session: 1-5) mixed measures ANOVA

Total locomotor activity		
Interaction:	MDMA dose × session	$F(2.63, 57.83) = 3.23$, $p = .035$, $\eta_p^2 = .128$
Simple main effect:	MDMA dose on session 1[1]	$F(1, 22) = 99.55$, $p < .001$, $\eta_p^2 = .819$
	MDMA dose on session 2[1]	$F(1, 22) = 79.79$, $p < .001$, $\eta_p^2 = .784$
	MDMA dose on session 3[1]	$F(1, 22) = 64.99$, $p < .001$, $\eta_p^2 = .747$
	MDMA dose on session 4[1]	$F(1, 22) = 128.20$, $p < .001$, $\eta_p^2 = .854$
	MDMA dose on session 5[1]	$F(1, 22) = 102.88$, $p < .001$, $\eta_p^2 = .824$
	Session on MDMA 10.0	$F(4, 44) = 3.18$, $p = .022$, $\eta_p^2 = .224$
Simple comparisons	No significant differences	
Centre locomotor activity		
Interaction:	MDMA dose × session	$F(2.57, 56.52) = 14.05$, $p < .001$, $\eta_p^2 = .435$
Simple main effect:	MDMA dose on session 1[1]	$F(1, 22) = 42.72$, $p < .001$, $\eta_p^2 = .660$
	MDMA dose on session 2[1]	$F(1, 22) = 16.52$, $p = .001$, $\eta_p^2 = .429$
	MDMA dose on session 3[1]	$F(1, 22) = 22.94$, $p < .001$, $\eta_p^2 = .510$
	MDMA dose on session 4[1]	$F(1, 22) = 40.96$, $p < .001$, $\eta_p^2 = .651$
	MDMA dose on session 5[1]	$F(1, 22) = 89.57$, $p < .001$, $\eta_p^2 = .803$
	Session on MDMA 10.0	$F(4, 44) = 16.60$, $p < .001$, $\eta_p^2 = .605$
Simple comparisons[2]:	Session 1 vs 4	$p = .005$
	Session 1 vs 5	$p < .001$
	Session 2 vs 4	$p = .037$
	Session 2 vs 5	$p = .025$
	Session 3 vs 4	$p = .009$
	Session 3 vs 5	$p = .003$
Peripheral locomotor activity		
Interaction:	MDMA dose × session	$p = .201$
Main effect:	MDMA dose	$F(1, 22) = 364.21$, $p < .001$, $\eta_p^2 = .943$
	Session	$p = .214$

[1] Level of significance accepted at $p < .01$.
[2] All other comparisons were not significant.

Table B3.
2 (eticlopride dose: 0.0, 0.3) × 5 (session: 1-5) mixed measures ANOVA

MDMA-produced total locomotor activity		
Interaction:	Etic dose × session	$p = .065$
Main effect:	Etic dose	$F(1, 21) = 272.95$, $p < .001$, $\eta_p^2 = .929$
	Session	$F(2.72, 57.17) = 3.10$, $p = .038$, $\eta_p^2 = .128$
MDMA-produced centre locomotor activity		
Interaction:	Etic dose × session	$F(2.69, 56.48) = 13.32$, $p < .001$, $\eta_p^2 = .388$
Simple main effect:	Etic dose on session 1[1]	$F(1, 21) = 32.95$, $p < .001$, $\eta_p^2 = .611$
	Etic dose on session 2[1]	$F(1, 21) = 9.69$, $p = .005$, $\eta_p^2 = .316$
	Etic dose on session 3[1]	$F(1, 21) = 15.88$, $p = .001$, $\eta_p^2 = .431$
	Etic dose on session 4[1]	$F(1, 21) = 28.60$, $p < .001$, $\eta_p^2 = .577$
	Etic dose on session 5[1]	$F(1, 21) = 75.09$, $p < .001$, $\eta_p^2 = .781$
MDMA-produced peripheral locomotor activity		
Interaction:	Etic dose × session	$p = .274$
Main effect:	Etic dose	$F(1, 22) = 271.20$, $p < .001$, $\eta_p^2 = .928$
	Session	$p = .202$

[1] Level of significance accepted at $p < .01$.

Table B4
2 (box zone: centre, periphery) × 5 (session: 1-5) repeated measures ANOVA

Percent change in MDMA-produced total locomotor activity		
Interaction:	Box zone × session	$F(4, 44) = 16.21$, $p < .001$, $\eta_p^2 = .596$
Simple main effect:	Box zone on session 1[1]	$p = .994$
	Box zone on session 2[1]	$p = .430$
	Box zone on session 3[1]	$p = .122$
	Box zone on session 4[1]	$F(1,11) = 17.97$, $p = .001$, $\eta_p^2 = .620$
	Box zone on session 5[1]	$F(1,11) = 44.50$, $p < .001$, $\eta_p^2 = .802$
	Session on centre[2]	$F(4,44) = 17.67$, $p < .001$, $\eta_p^2 = .616$
	Session on periphery[2]	$F(4,44) = 3.29$ $p = .019$, $\eta_p^2 = .230$
Simple comparisons (centre)[3]:	Session 1 vs 4	$p < .001$
	Session 1 vs 5	$p < .001$
	Session 2 vs 4	$p < .030$
	Session 2 vs 5	$p < .029$
	Session 3 vs 4	$p < .002$
	Session 3 vs 5	$p < .004$
Simple comparisons (periphery):	No significant differences	

[1] Level of significance accepted at $p < .01$.
[2] Level of significance accepted at $p < .025$.

Table B5
2 (eticlopride dose: 0.0, 0.3) × 5 (session: 1-5) mixed measures ANOVA

Basal rearing activity		
Interaction:	Etic dose × session	$p = .708$
Main effect:	Etic dose	$p = .055$
	Session	$p = .758$

Table B6
2 (MDMA dose: 0.0, 10.0) × 5 (session: 1-5) mixed measures ANOVA

Rearing activity		
Interaction:	Etic dose × session	$p = .708$
Simple main effect:	Etic dose	$p = .055$
	Session	$p = .758$
	MDMA dose on session 1[1]	$p = .098$
	MDMA dose on session 2[1]	$p = .054$
	MDMA dose on session 3[1]	$F(1, 22) = 15.18$, $p = .001$, $\eta_p^2 = .408$
	MDMA dose on session 4[1]	$F(1, 22) = 32.44$ $p < .001$, $\eta_p^2 = .596$
	MDMA dose on session 5[1]	$F(1, 22) = 22.72$, $p < .001$, $\eta_p^2 = .606$
	Session on MDMA 10.0	$F(2.37, 26.09) = 21.64$, $p < .001$, $\eta_p^2 = .663$
Simple comparisons[2]:	Session 1 vs 3	$p = .001$
	Session 1 vs 4	$p < .001$
	Session 1 vs 5	$p < .001$
	Session 2 vs 3	$p = .004$
	Session 2 vs 4	$p < .001$
	Session 2 vs 5	$p = .002$

[1] Level of significance accepted at $p < .01$.
[2] All other comparisons were not significant.

Table B7
2 (eticlopride dose: 0.0, 0.3) × 5 (session: 1-5) mixed measures ANOVA

MDMA-produced rearing activity		
Interaction:	Etic dose × session	$F(2.39, 50.16) = 18.95$, $p < .001$, $\eta_p^2 = .474$
Simple main effect:	Etic dose on session 1[1]	$p = .034$
	Etic dose on session 2[1]	$p = .032$
	Etic dose on session 3[1]	$F(1, 21) = 16.38$, $p = .001$, $\eta_p^2 = .438$
	Etic dose on session 4[1]	$F(1, 21) = 31.32$, $p < .001$, $\eta_p^2 = .599$
	Etic dose on session 5[1]	$F(1, 21) = 35.57$, $p < .001$, $\eta_p^2 = .629$

[1] Level of significance accepted at $p < .01$.