

The role of trait impulsivity and novelty-seeking as predisposing  
factors to the acquisition and reinstatement of  
MDMA self-administration

By

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## **Abstract**

It has been suggested that the response to novelty and impulsivity predict the latency to acquisition and maintenance of drug self-administration, respectively. The aim of this thesis was to examine the relationship between these two traits and (1) the latency to acquisition and (2) maintenance (drug seeking) of 3,4-methylenedioxymethamphetamine (MDMA) self-administration. Impulsivity, measured as premature responding on the 5-choice serial reaction time task (5-CSRTT), and novelty seeking, measured as the locomotor response in a novel environment, were measured prior to self-administration. Due to characteristics of the rat strain and test equipment the 5-CSRTT was configured in the first part of this study and modified from the standard version. Following training in this task animals were implanted with a siliastic catheter and were subsequently screened for their response to a novel environment prior to MDMA self-administration. Latency to acquisition was determined as the number of test sessions required to self-administer an initial criterion of 90 infusions of 1.0 mg/kg/infusion as well as an additional 150 infusions of 0.5 mg/kg/infusion MDMA. For some rats, the ability of MDMA (0, 5.0 or 10.0 mg/kg, IP) to produce drug seeking was subsequently measured and for others, impulsivity was again measured following self-administration. Novelty seeking predicted cocaine self-administration but was not significantly correlated with either the acquisition or drug-seeking measures of MDMA self-administration. Impulsivity was not significantly correlated with the latency to acquire self-administration of MDMA but was significantly and positively correlated with the magnitude of MDMA produced drug-seeking. Furthermore, MDMA self-administration produced a number of notable, but transient, deficits in the 5-CSRTT; there was an increase in omission rate and a delayed

increase in premature responses in particular. These findings suggest that impulsivity, but not sensation seeking, might be a risk factor for the development of compulsive drug-seeking following withdrawal from MDMA self-administration. A surprising finding from this study was a high acquisition rate amongst rats that acquired the 5-CSRTT prior to self-administration. This difference was examined in a separate set of experiments. This effect could not be explained by an effect of handling, food restriction, or exposure to sweetened condensed milk and might possibly be due to differences in instrumental learning.

## **I. General introduction**

### **Introduction to MDMA**

#### *History*

3,4-methylenedioxymethamphetamine (MDMA; “Ecstasy”) is a ring-substituted amphetamine derivative that is also structurally related to the hallucinogen mescaline (Green, Mehan, Elliott, O'Shea, & Colado, 2003). It was originally patented in 1914 by the German pharmaceutical company, Merck, as a precursor for therapeutically active compounds, but otherwise was unremarkable for many decades. A few pharmacological tests in laboratory animals were conducted by the US military in the 1950s (Hardman, Haavik, & Seevers, 1973) before the first report of MDMA's psychoactive effects on human was published in the late 1970s (Shulgin and Nichols, 1978). Around the same time, MDMA started being used in psychotherapy with patients who experienced difficulties with emotions, empathy and self-esteem (Greer & Tolbert, 1986; Grinspoon & Bakalar, 1986). At this time, MDMA also became a drug of choice for “clubbers” and in the U.S. MDMA became classified as a Schedule 1 drug owing to its purported high potential for abuse, lack of clinical application, lack of accepted safety for use and evidence that related amphetamine derivatives (e.g. MDA) caused serotonergic nerve terminal degeneration in laboratory animals (Ricaurte, Bryan, Strauss, Seiden, & Schuster, 1985).

Despite its illegal status MDMA became a popular recreational drug often linked to the “rave” or “techno” scene. Increased academic interest is evident by the increase

of scholarly publications per year over the last few decades. The number of publications ranges from none in 1984, 2 in 1985, over 100 in 2000 and 281 in 2011 (Pubmed [searchwords: MDMA; year], June 2012).

*Epidemiology, subjective effects, and patterns of use*

MDMA is usually consumed orally (in pill form) or via insufflation. The content of pills varies in dose and purity, but usually one ecstasy tablet contains between 20 and 150 mg of MDMA (Ziporyn, 1986; Morefield et al. 2011; Cole et al. 2002; Wood et al. 2011). Effects include a relaxed euphoric state, emotional openness, empathy, reduction of negative thoughts, a decrease in inhibitions and an enhanced perception of colour and sounds (Hegadoren, Baker, & Bourin, 1999; Liechti, Baumann, Gamma, & Vollenweider, 2000; Morgan, 2000; Peroutka et al., 1988). Several physiological effects are produced, including tachycardia, elevated blood pressure, nausea, chills, sweating, tremor, jaw clenching, bruxisms, urinary urgency, tension, nystagmus, insomnia and dry mouth (McCann, Slate, & Ricaurte, 1996; Peroutka et al., 1988). When taken orally the physiological and subjective effects begin to manifest approximately 15 minutes following ingestion. Plasma concentrations peak at about 2 hours following ingestion (Kolbrich et al. 2008; de la Torre et al. 2000 a; 2000 b). The half-life is about 3 to 5 hours.

Pharmacokinetic studies revealed a non linear increase in plasma MDMA with increasing doses that are within the range used recreationally (De la Torre et al, 2000a; Kolbrich et al, 2008; Mas et al, 1999; Mueller et al, 2009; Farre et al, 2004). When MDMA dose was increased by a factor of 3, peak plasma concentrations increased by a factor of 6, thus this pattern of non-linearity in pharmacokinetics of MDMA is evident in the relationship between drug and plasma levels, in that small increases in dose lead



to relatively large changes in plasma levels (Mas et al., 1999; de la Torre et al., 2000a, 2000b).

The stereoisomers of MDMA have different potencies, pharmacokinetics and effects on neurotransmitter release but MDMA is usually consumed as a racemic mixture of the (R)-enantiomer and the (S)-enantiomer in a 1:1 ratio (Pizarro et al, 2004) and is metabolised mainly in the liver. The (+) isomer has a faster clearance; therefore the drug-induced effects are shorter in duration (Fitzgerald et al., 1990).

According to the most recent World Drug Report, prevalence of MDMA use is high, especially amongst young people (WDR, 2011). Some users frequently consume large amounts (Scheier et al. 2008; Thomasius et al. 2005) and some meet DSM criteria for dependence (Cottler, Leung, & Abdallah, 2009; Cottler, Womack, Compton, & Ben-Abdallah, 2001; Hanson & Luciana, 2004; Thomasius et al., 2005). There are no specific criteria in the DSM for MDMA dependence and so most studies use the more general criteria for substance abuse and dependence. Prevalence estimates vary considerably between studies but between 20% and 60% of users meet these criteria for dependence (Hando et al. 1997; Schuster et al. 1998; Cottler et al. 2001; Yen and Hsu, 2007)<sup>1</sup>.

Most ecstasy users are 15-34 year olds and many of them (66%) are 18 or older. First time use in the USA is at an average age of 20.2 years (WDR, 2011). In 2009 the UNDOC estimated the global annual prevalence to be between 0.2% and 0.6% of the adult population corresponding to approximately 11 to 28 million people who used ecstasy at least once in the previous year. Oceania, in particular Australia and New Zealand, have the highest prevalence rate of ecstasy use in the world with 3.6% to 4% annual prevalence of the adult population.

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<sup>1</sup>It also has to be noted that many of those studies recruited already heavy MDMA users (Cottler et al., 2009; Cottler et al., 2001) and the bias of the sample might distort the true prevalence of ecstasy dependence.

Despite the relatively high annual and life-time prevalence of MDMA use, it is important to note that only a small percentage of users progress to abuse and dependence. Approximately 15.1% (37.9 million) of the US population that were 12 years or older consumed nonmedical or illicit drugs in the past year, with approximately 2.8% (7.1 million) progressing to dependence (Center for Behavioral Health Statistics and Quality, 2012). These statistics raise some intriguing questions concerning factors that might predispose some individuals to drug dependence.

### *Vulnerability to drug addiction*

Drug addiction is often used synonymously with substance dependence as defined by the DSM-IV (Diagnostic Statistical Manual of Mental Disorders, 4<sup>th</sup> edn., text revision; American Psychiatric Association, 2000). The DSM-IV-TR (2004) defines substance dependence as “a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period”:

(1) Tolerance<sup>2</sup> towards the pharmacological effects of drugs, (2) withdrawal<sup>3</sup> when the substance is no longer available, (3) the substance is often taken in larger amounts or over a longer period than was intended, (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use; (5) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects, (6) important social, occupational, or recreational activities are given up or

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<sup>2</sup> Tolerance describes a regulatory process between an organism and a pharmacological compound in a compensatory manner. The effects of the compound decrease with repeated exposure or can only be maintained at an initial level if the dose is increased.

<sup>3</sup> Withdrawal can best be observed after a sudden offset of a drug and is expressed in a range of vegetative effects which usually are contrary to the initial effects of the drug. This effect is most pronounced for opiates, alcohol and barbiturates.

reduced because of substance use, (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. Substance dependence can further exist with physiological (evidence of tolerance or/and withdrawal symptoms) or without physiological dependence<sup>4</sup>.

Drug dependence is a progressive disorder and several key phases in this development have been identified, such as the initiation of drug-taking (are some individuals more susceptible to the initial reinforcing properties of addictive drugs?), the development of compulsive drug-taking (escalation and loss of control over drug-taking behaviour) and relapse (the inability to refrain from drug-seeking and drug-taking after a period of abstinence). Various factors have been suggested to contribute to these phases describing the development of drug dependence.

Vulnerability to drug dependence can be influenced by a number of biological, environmental or cultural variables. Of particular relevance to this thesis are the biological and genetic factors that underlie the initial response to drugs of abuse and the neurobiological changes following long-term drug exposure. Individuals more or less vulnerable to dependence might differ in their response to the pharmacological properties of drugs of abuse. The variability in this initial response might form the basis for the differences in vulnerability and thus provide a neurobiological basis possibly promoting or constraining neuroadaptations caused by repeated exposure to certain substances. Consequently, those neuroadaptations might in turn facilitate the development of drug dependence (Koob et al. 1998). These various vulnerability factors often interact in the expression of vulnerable phenotypes or traits which can be easily observed and studied in relation to drug dependence.

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<sup>4</sup> This psychological dependence occurs with all drugs of abuse. It means the strong, irresistible desire, that is, craving for the abused drug to achieve the subjective positive effects of the drug as well as to avoid the negative effects produced by withdrawal.

Indeed, some studies have suggested that certain traits might be linked to drug abuse (Compton et al. 2007; Carroll et al. 2009). Individual factors such as depression and aggression, stress, age, sex and hormonal effects, impulsivity, dietary preferences, sensation seeking, avidity for exercise, and impoverished vs. enriched environments play a role in predicting drug abuse (Schenk et al. 1983; Goeders, 2003; Miczek et al., 2008). Amongst those, the impact of impulsivity and sensation seeking on drug dependence has been investigated and evidence from human studies link these personality traits to drug abuse and addiction (Chakroun et al. 2004; Dawe & Loxton 2004; Sher et al. 2000; Adams et al. 2003). It has been suggested that these traits share a common neurobiological basis that also mediates various aspects of drug dependence (Piazza et al. 1989; Dalley et al. 2007; Everitt et al. 2008).

The current project aims to determine the psychobiological basis of vulnerability to MDMA abuse and will focus on the contribution of impulsivity and novelty-seeking (a core feature of sensation seeking) to the initiation and maintenance of MDMA self-administration.

### *Pharmacological mechanisms of MDMA*

Acute administration of MDMA produces marked increases in synaptic levels of monoamines while MDMA was more potent in releasing Serotonin (5HT) than dopamine (DA) and norepinephrine (NE) (Fitzgerald & Reid, 1993; McKenna et al, 1991; Gough et al., 1991; White et al., 1996; Lyles & Cadet, 2003; Colado et al., 2004; Green et al., 2003). 5HT was released in a dose-dependent manner following addition of MDMA to brain slices (Berger, Gu, & Azmitia, 1992; Johnson, Hoffman, & Nichols, 1986; Koch & Galloway, 1997; Schmidt, 1987) and synaptosomal preparations (Berger et al., 1992; O'Loinsigh, Boland, Kelly, & O'Boyle, 2001). Numerous *in vivo*

microdialysis studies have documented increased synaptic 5HT overflow following exposure to MDMA (Gough et al, 1991; Yamamoto & Spanos, 1988; Hiramatsu et al, 1991; Nash & Nichols, 1991; Reveron et al, 2010; Estaban et al, 2001; Baumann et al, 2008; Sabol & Seiden, 1998; Gudelsky & Nash, 1996; Kehr et al, 2012) and this effect was dose-dependent (Gudelsky & Nash, 1996). MDMA also produces dose-dependent increases in synaptic DA but to a lesser extent than synaptic 5HT. A low dose of MDMA (1.5 mg/kg) which had an impact on 5HT levels failed to increase DA but a higher dose (7.5 mg/kg) increased both, 5HT and DA, 30-fold and 5-fold respectively (Baumann et al. 2008). Following an intravenous (i.v.) injection of MDMA (3mg/kg), extracellular levels of 5HT increased to about 1200% of baseline, and extracellular DA levels peaked at 500% of baseline (Reveron et al. 2010).

An important role of the 5HT transporter (SERT) in the neurochemical effects of MDMA has been demonstrated. MDMA-produced 5HT overflow in the striatum (Gudelsky & Nash, 1996) and hippocampus (Mechan et al., 2002) was markedly decreased by pretreatment with the serotonin selective reuptake inhibitor (SSRI), fluoxetine (Hekmatpanah & Peroutka, 1990; Berger et al., 1992; Rudnick & Wall, 1992). Similar roles of the DA (DAT) or norepinephrine (NET) transporters in the MDMA-produced increases in synaptic levels of DA and NE have also been demonstrated (Nash & Brodtkin, 1991; Shankaran et al., 1999; Fitzgerald & Reid, 1990; Schmidt et al.1987; Gu & Azmitia, 1993). Thus, MDMA produces efflux of monoamines through transporter-mediated exchange (Berger et al, 1992; Hekmatpanah & Peroutka, 1990; Yamamoto & Spanos, 1988; Rudnick & Wall, 1992; Fitzgerald & Reid, 1990) and increases cytoplasmic levels of monoamines via interaction with the vesicular monoamine transporter (VMAT), (Rudnick & Wall, 1992; Bogen et al, 2003). The increased synaptic levels of monoamines activates several receptor subtypes (White et al. 1996) including 5HT<sub>1</sub> and 5HT<sub>2</sub> receptors, D<sub>1</sub>- and D<sub>2</sub>-like receptors but

also  $\alpha 1$ -  $\alpha 2$ - and  $\beta 2$ -adrenergic receptors, muscarinic and histamine receptors. MDMA also increases acetylcholine (Fischer et al. 2000) and inhibits gamma amino butyric acid (GABA) activity (Yamamoto et al. 1995).

MDMA increases synaptic levels of DA via direct mechanisms involving the DAT, as previously described, and also by indirect mechanisms. One such indirect mechanism is an inhibitory effect of 5HT on DA neurotransmission. Several studies have shown that 5HT modulates DA release via activation of specific receptor subtypes (Porras et al. 2002; Alex et al. 2005; Bubar et al. 2011). Direct infusion of 5HT<sub>2</sub> receptor agonists into the nucleus accumbens or striatum increased DA levels in the striatum and substantia nigra (Benloucif & Galloway, 1991; Parsons and Justice, 1993). Conversely, it has also been found that the 5HT<sub>2</sub> receptor antagonist, ritanserin, decreased MDMA-induced DA release in these areas (Yamamoto et al., 1995). However, activation of different 5HT<sub>2</sub> receptors can have different effects on dopamine release. For example, 5HT<sub>2A</sub> receptor agonists increased (Lucas & Spampinato 2000, Yan, 2000), and antagonists decreased (Lucas & Spampinato 2000, Schmidt et al 1994) MDMA-produced dopamine increases. Effects of activation of the 5HT<sub>2C</sub> receptor produced opposite effects on DA release. Indeed, antagonists administered locally into the ventral tegmental area (VTA) disinhibited nucleus accumbens (NAcc) DA release (Bankson & Yamamoto 2004). This might be due to GABAergic mechanisms as GABA is known to decrease DA cell firing in the VTA (Kiyatkin & Rebec 1998). 5HT<sub>2C</sub> receptors located on non-DAergic (presumably GABA) neurons in the VTA increase GABA transmission (Stanford & Lacey 1996). Therefore, 5HT<sub>2C</sub> receptors may decrease DA cell firing through increases in GABA release in the VTA.

It has further been suggested that competitive antagonism of the SERT, which results in a reduction of MDMA induced 5HT also contributes to the effects of MDMA on DA release (Gough, Ali, Slikker, & Holson, 1991; Koch & Galloway, 1997;

Yamamoto & Spanos, 1988; Crespi, Mennini, & Gobbi, 1997; Johnson et al., 1986; Schmidt, 1987). For example, pre-treatment with the selective serotonin reuptake inhibitor fluoxetine, attenuated MDMA-induced elevations of striatal dopamine (Koch & Galloway 1997).

These acute effects of MDMA on neurotransmitter release have several short and long-term consequences that might become increasingly important with chronic use. For example, the increase in 5HT following acute MDMA is followed by a reduction in brain 5HT levels. This effect has been confirmed by evidence of a marked decrease in 5HT concentration from brain tissue samples of rats that received acute exposure to MDMA, (Aguirre, Galbete, Lasheras, & Del Rio, 1995; Colado & Green, 1994; Connor et al., 1998; Gough et al., 1991; Logan, Lavery, Sanderson, & Yee, 1988; McKenna & Peroutka, 1990; Schmidt, Wu, & Lovenberg, 1986; Stone, Hanson, & Gibb, 1987). Following chronic administration schedules using multiple high dose exposure, the decrease in 5HT tissue levels was more pronounced (Mokler et al. 1987; Battaglia et al. 1988; Ricautre et al. 1988; Clemens et al. 2007). Recently, decreased tissue levels of 5HT levels have also been shown following chronic MDMA self-administration (Schenk et al. 2007; Schenk et al. 2011a; Do & Schenk 2011). The consequences of this 5HT deficit following repeated MDMA exposure on the continued consumption and dependence have yet to be examined. Given the interactions between 5HT and DA it seems possible that MDMA produced changes in 5HT would also influence DA neurotransmission. Indeed, deficits in 5HT produced by the neurotoxin 5,7-DHT altered DA neurotransmission in the cerebral cortex (Ashby et al. 1994; Ferron et al. 1982). One recent study suggested an inhibitory influence of 5HT on the firing rate of DA neurons in the VTA which was reversed by a 5HT lesion (Guiard et al. 2008). Finally, another study showed that pretreatment with MDMA that resulted in

73% reduction in 5HT attenuated the inhibitory effects of DA on excitability of NAcc cells (Obradovic et al. 1998).

To further study these effects and advance our understanding of mechanisms underlying drug taking and dependence clinical research in human subjects is often confounded by polydrug use and limited by ethical constraints. As an example, addicts often have a long history of drug taking and rarely limit their consumption to one drug of abuse. Consequently, neural adaptations and numerous neurochemical interactions between different drugs of abuse prevent a clear attribution of consequences of drug-taking to the effects of one particular drug. Furthermore, despite advances in neuroimaging techniques it is difficult if not impossible to gain insight into neural mechanisms involved in a drug's action in human subjects. Animal models, however, provide control over various factors that can confound human studies. Drug self-administration paradigms are particularly useful as they not only allow an estimation of the reinforcing efficacy of a substance but also allow an estimation of the abuse potential of drugs and the ability to study all aspects of drug-taking from initiation through to dependence.

### *Self-administration*

The development of the chronic indwelling intravenous catheter (Weeks, 1962) provided a means by which laboratory animals could learn to perform an operant to intravenously self-administer drugs (Clark, Schuster, & Brady, 1961; Deneau, Yanagita, & Seevers, 1969; Weeks, 1962). This provided, for the first time, a mechanism of self-administration that was not confounded by factors that sometimes limited other methods



of drug self-administration. A wealth of studies during the 1960s and 1970s established that results using the intravenous procedure provided good construct validity and appealing face validity (Deneau et al., 1969; Headlee, Coppock, & Hichols, 1955; Schuster & Thompson, 1969; Pickens et al. 1967; Pickens & Harris 1968; Pickens & Thompson 1968; Davis et al. 1968; Yanagita & Takahashi 1973; Kramer et al. 1967) and, importantly, the neurobiological substrates underlying animal and human drug self-administration are largely comparable (Bozarth & Wise, 1983; Cami & Farre, 2003; Di Chiara & Imperato, 1988; Everitt & Robbins, 2005; Holman, 1994; Hommer, Bjork, & Gilman, 2011; Ito, Dalley, Robbins, & Everitt, 2002; Kankaanpaa, Meririnne, Lillsunde, & Seppala, 1998; Koob, 1992a, 1992b; Liebman & Butcher, 1973; Munzar, Baumann, Shoaib, & Goldberg, 1999; Philibin, Hernandez, Self, & Bibb, 2011; Rothman & Baumann, 2006; Suto, Wise, & Vezina, 2011; Volkow, Fowler, & Wang, 1999; Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow, Fowler, Wang, & Swanson, 2004; Volkow, Wang, et al., 1999; Wise, 1984, 1996). The validity of the procedure is further demonstrated by the finding that, with few exceptions, drugs that are abused by humans are readily self-administered by laboratory animals whereas drugs that show limited abuse potential are not self-administered by animals (Deneau et al., 1969; Headlee, Coppock, & Hichols, 1955; Schuster & Thompson, 1969). Self-administration, therefore, is a useful tool for determining the abuse potential of a drug.

Most self-administration paradigms reinforce correct performance of an operant with a drug infusion. Simple choice procedures are often used so that depression of one (active) lever results in a drug infusion, while depression of the other (inactive) lever has no programmed consequence. Development of a preference for the active lever indicates the positively reinforcing properties of the drug (Brady & Griffiths, 1976; Griffiths, Brady, & Bigelow, 1981; Griffiths, Brady, & Snell, 1978) and has been shown for several drugs of abuse, including psychostimulants, opiates and ethanol (Goldberg et

al. 1971; Downs & Woods 1974; Pickens & Thompson 1968; Goldberg & Kelleher 1976; Goldberg 1973; Balster et al. 1976; Pickens et al. 1967; Pickens & Harris 1968; Balster & Schuster 1973; Yokel & Pickens 1973; Goettestam & Anderson 1975; Griffith et al. 1976; Weeks 1962; Denau et al. 1969; Jones & Prada 1973; Collins & Weeks 1965; Winger & Woods 1973; Kelleher 1975; Davis et al. 1968; Yanagita & Takahashi 1973; Winger et al. 1975; Ledent et al. 1999; Martellotta et al. 1998). When the drug solution is replaced with saline, responding decreases within a few days and can be reinstated by reintroduction of the drug (de Wit & Stewart, 1981; Yokel & Pickens, 1973).

When given unlimited access to the drug, intake patterns vary with drug class (Deneau et al. 1969). For example, stimulants are consumed in binge-like patterns separated by periods of abstinence (Pickens & Harris 1968; Yokel & Pickens 1973; Johanson et al. 1976) which markedly resembles patterns of use during stimulant addiction (Kramer et al. 1967). Opiates, on the other hand maintain constant but moderate consumption in the absence of voluntary periods of abstinence, like human opiate addicts (Deneau et al. 1969; Harrigan & Downs 1978). With nearly all intravenously self-administered drugs the risk of excessive consumption to the point of acute toxicity or death during periods of unlimited access is present. For psychostimulant self-administration the fatality rate is particularly high (Deneau et al. 1969; Yokel & Pickens 1973). To minimize the risk of acute and chronic toxicity when the self-administered drug is freely available, restrictions can be placed on drug availability. Typically, drug is made available for self-administration for only a few (1 to 6) hours during daily sessions. In addition, response requirements for drug injections are often increased beyond a single response. When drug access is limited drug intake is usually stable from session to session but response rates will still show the characteristic patterns of the respective drug class (Yokel & Pickens, 1973).

A feature of drug dependence is that stimuli paired with drugs of abuse can, following substantial numbers of pairings, become conditioned reinforcers themselves capable of maintaining drug-seeking via Pavlovian processes. Such a stimulus paired with a drug injection could be a light or tone, and will be presented on depression of the active lever whereas responses on the inactive lever have no consequences throughout the experiment (Davis & Smith 1976). In one study an anise-flavoured solution of etonitazene (an opiate agonist), was the only available drinking solution for a group of non-opiate-dependent rats (Wikler et al. 1971). Months after the initial experiment animals consumed twice as much anise-flavored water as control rats, when they were presented with a two-bottle choice situation. This study first suggested that previously neutral stimuli can acquire reinforcing properties when paired with reinforcing drugs. These effects have also been demonstrated for intravenous self-administration, where a previously neutral stimulus can also acquire conditioned reinforcing properties when paired with a drug infusion (Davis & Smith, 1976). Furthermore, conditioned reinforcing effects of neutral stimuli can also be observed when the drug administration is not contingent on the animal's behaviour, as long as the stimulus precedes the drug injection (Davis & Smith 1976). It can subsequently maintain responding in the absence of drug injections and thus provide a measure of the reinforcing value of these stimuli and the neural substrate for these effects appears to be the release of DA to the nucleus accumbens (Kelley & Delfs 1991a, 1991b).

Dose-response curves for drug self-administration are typically in the shape of an inverted "U". Thus, both low and high doses fail to reinforce high rates of operant responding under a fixed ratio schedule of reinforcement. As the dose of drug is increased from the subthreshold dose, responding increases and then decreases again as the dose is further increased. Thus, there are two limbs to the dose-effect curve; an

ascending and descending limb (Carroll & Lac, 1997; Goldberg, Hoffmeister, Schlichting, & Wuttke, 1971; Griffiths, Winger, Brady, & Snell, 1976; O'Brien & Gardner, 2005; Schenk & Partridge, 1997; Yokel & Pickens, 1973; Yokel & Wise, 1976). Initial studies suggested that responding changed as a function of dose on the descending limb of the dose-effect curve in order to maintain constant blood levels of drug (Pickens et al. 1968). In other words, blood-brain levels of a drug were titrated through compensatory responding (Hurd et al 1989, Pettit & Justice 1989, Pettit & Justice 1991, Ranaldi et al 1999, Wise et al 1995a, 1995b). In one elegant study of rats self-administering d-amphetamine (AMPH) an operant response to self-administer an infusion was produced when blood levels fell below 0.2mg/ml (Yokel & Pickens 1973). Similar findings were produced during cocaine self-administration when responding was associated with decreased brain levels of DA and cocaine (Wise et al, 1995a, 1995b).

Drug self-administration has been used as a primary research avenue to identify the mechanisms underlying the development and maintenance of drug dependence. To this end, effects of pharmacological probes and selective lesions have helped to identify the brain systems that underlie the initiation and maintenance of drug taking. In some cases, shifts in the dose-effect function have been measured and in others responding maintained by single doses of the self-administered drug have been determined.

### *Neural substrates of drug self-administration*

The primary pharmacological targets of drugs of abuse vary considerably, but a common effect is an enhancement of synaptic levels of DA (Di Chiara and Imperato, 1988). A wealth of data suggests that this effect underlies the positively reinforcing

effects of drugs of abuse. *In vivo* microdialysis studies consistently demonstrate an increase in extracellular DA in the NAcc shell during active self-administration of opiates, cannabinoids, nicotine, amphetamines and cocaine and ethanol (Di Chiara & Imperato, 1988). DA agonists are self-administered by laboratory animals (Deneau et al. 1969; Schuster & Thompson 1969) whereas inhibition of DA synthesis (Pickens et al. 1968; Wilson & Schuster 1974) or administration of high dose DA antagonists (Yokel & Wise 1975, Woolverton, 1986; Rassnick et al. 1992; Richardson et al. 1993) decreased self-administration. Interestingly, when given low doses of DA antagonists responding for psychostimulant self-administration increased, presumably, in an attempt to keep drug intake constant (Pickens et al. 1968; Wilson & Schuster 1974; Woolverton 1986). When DA synthesis or receptors were completely blocked by a dose high enough responding first increased and finally stopped. The same pattern of responding was found when, for example, amphetamine infusions were terminated (Pickens & Harris, 1968). It represents classical extinction of responding during non-reinforcement and suggests that the reinforcing effects of drugs are mediated by DAergic substrates.

The integrity of the mesocorticolimbic DA system, in particular, is critical to self-administration (Wise 1989; Robbins & Everitt 1996; Berridge & Robinson 1998; Di Chiara 1999; Kelley & Berridge 2002). This system is composed of two major pathways: projections from neurons of the VTA extend to limbic structures including the amygdala, the ventral pallidum, the hippocampus and the NAcc (mesolimbic pathway) and cortical structures including the prefrontal cortex (PFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) (mesocortical pathway) (Cami & Farre, 2003). The mesolimbic structures, in particular the DA projections to the NAcc mediate the primary reinforcing effects of drugs and the potentiation of conditioned responses (Di Chiara, 2002; Fuchs, Eaddy, Su, & Bell, 2007; Fuchs et al., 2005; Rogers & See, 2007; See, 2005; Volkow, Fowler, & Wang, 2003).

Many drugs of abuse were self-administered directly into the amygdala, the NAcc, the PFC and the OFC, and the VTA (Bozarth & Wise, 1981, 1982; Chevrette, Stellar, Hesse, & Markou, 2002; Gatto, McBride, Murphy, Lumeng, & Li, 1994; McBride, Murphy, & Ikemoto, 1999; Olds, 1982; Phillips, Mora, & Rolls, 1981; Rodd et al., 2004; Shin, Qin, Liu, & Ikemoto, 2008; van Ree & de Wied, 1980). The NAcc has been hypothesised to play a key role in the reinforcing effects of drugs since drugs of abuse, including MDMA (Cadoni et al., 2005; O'Shea et al., 2005; Yamamoto & Spanos, 1988) increase extracellular DA concentration (Di Chiara & Imperato 1988; Pontieri et al. 1995, 1996; Tanda et al. 1997). The NAcc plays a key role in motor performance (receiving inputs from motor structures) as well as in reward, motivation, and affective disorders (receiving its main inputs from the limbic structures, which are critical for affective processing; Basar et al. 2010). In particular the core region has been linked to motor functions while the shell region has been implemented in the regulation of affective processes because of its projections to the extended amygdala (Alheid & Heimer 1988; Heimer et al. 1991).

In addition, other neurotransmitter systems may also contribute to the reinforcing effects of drugs of abuse but these effects might be specific for certain drug classes. For example, lesions of the NAcc alone did not attenuate opioid or alcohol self-administration despite substantial depletions of DA (Dworkin, Guerin, Co, Goeders, & Smith, 1988; Ettenberg, Pettit, Bloom, & Koob, 1982; Koob, 2006; Pettit, Ettenberg, Bloom, & Koob, 1984; Rassnick, Stinus, & Koob, 1993). In contrast, these lesions disrupted AMPH and cocaine self-administration (Lyness et al. 1979; Roberts & Koob 1982). Thus, it is likely that different types of drugs have specific neurochemical mechanisms for self-administration. Furthermore, the substrates and neurochemical mechanisms mediating self-administration can conversely be modified by drugs of abuse.

Repeated exposure to drugs of abuse can lead to persistent neuroadaptations at molecular, cellular, and neural levels (Nestler et al. 1993; Robinson & Berridge 2000; Vanderschuren & Kalivas 2000; Everitt & Wolf 2002) specifically in the VTA, the NAcc and other brain reward regions (Nestler, 2005). There are numerous adaptations that accompany the repeated exposure to different drugs, some specific to certain drugs of abuse, but all are common in their produced alterations of DA transmission (Di Chiara et al. 2004). Decades of findings have tied these neuroadaptations to behavioural responses related to drug addiction and have been reviewed to the fullest extent elsewhere (Feltenstein & See 2008; Wolf 2002; Koob & Le Moal 2008; Koob & Volkow 2010; Koob et al. 1998; Nestler 2005). A few examples of these modifications are briefly discussed in the following section.

Chronic drug exposure, for example, induce a long-term potentiation (LTP)-like state in VTA DA neurons (Saal et al. 2003; Borgland et al. 2004; Thomas & Malenka 2003) which is mediated via increased responsiveness of glutamate receptors and has been related to a sensitized behavioural response to drugs of abuse (Thomas & Malenka 2003; Carlezon & Nestler 2002). Conversely, stimulant drugs cause a long-term depression (LTD)-like state in NAcc neurons (Thomas & Malenka, 2003). A further change following chronic drug exposure is an increase in tyrosine hydroxylase (TH), the rate-limiting enzyme in DA biosynthesis in the VTA (Nestler 1992; Grimm et al. 2003; Beitner-Johnson & Nestler, 1991; Persico et al., 1993; Sorg et al., 1993; Vrana et al., 1993; Ortiz et al., 1995; Masserano et al., 1996). This upregulation of TH might contribute to the complex effects that drugs exert on DAergic transmission and has been attributed to the activation of the transcription factor CREB (cAMP response element binding protein) (Olson et al. 2005).

Several drug induced changes in transcription factors have also been reported with a special focus on CREB and  $\Delta$ FosB which in turn have been linked to behavioural

plasticity following chronic drug exposure (Olson et al. 2005; Walters et al. 2005a, 2005b; Nestler et al. 2001; McClung et al. 2004). For example, the accumulation of  $\Delta$ FosB in the NAcc has been associated with the development of sensitization (Nestler et al. 2001; McClung et al. 2004) as overexpression increased the behavioural response to cocaine while blockade of  $\Delta$ FosB function decreased such a response. A further consequence of chronic drug exposure is a reduced amount of neurofilament proteins within the VTA (Nestler, 1992; Bolanos & Nestler, 2004) which may be a biochemical marker of morphological changes to VTA neurons induced by drugs of abuse. These morphological changes (such as reduced size of VTA cell bodies) have only been documented for opiates and have been suggested to be related to impaired axonal transport from the VTA to the NAcc.

Behavioural changes that might arise from such neuroadaptations are thought to underlie the transition from initial drug-taking to drug dependence. For example, the impulsive and compulsive features of stimulant addiction have been attributed to a profound dysfunction in cortical control over the NAcc (Kalivas et al. 2005). In support of this hypothesis it has been shown that ibotenic acid lesion of the dorsal PFC disrupted the expression of behavioural sensitization, a feature of drug dependence (Pierce et al. 1998; but see Li & Wolf 1997) while impulsivity can be induced by lesions of the medial PFC area (Pezze et al. 2009). This dysfunction of cortical control over the NAcc in turn has been attributed to abnormal dopaminergic and glutaminergic innervations of the NAcc from frontal cortical regions (Kalivas et al. 2005).

Rats sensitized to cocaine show an increased glutamate response in the NAcc core in response to a cocaine challenge injection (Pierce et al. 1998; 1996). The latter may be a result from a decrease in cortical DA transmission (Sorg et al. 1997). Thus, reduction in PFC DA might disinhibit excitatory projections to the NAcc producing an increase in glutamate transmission. Indeed, due to the inhibition of D2 DA receptors in



the PFC caused by withdrawal (Bowers et al. 2004) drug associated stimuli, such as the drug itself or stress, will preferentially activate D1 DA receptors which in turn will promote behaviour orientated towards particularly strong stimuli (e.g. drug associated cues) through strong activation of the PFC through drug-induced DA release. Predominance of D1 DA receptor signalling in the PFC results in inhibition of PFC output (this has been labelled hypofrontality and describes a reduced motivation to respond to non-drug related stimuli). Drug associated stimuli will be more potent in activating PFC networks which will stimulate PFC pyramidal cells. These cells will encounter homeostatic deficits in glutamate synapses in the NAcc which in turn strengthen the behaviour making it difficult to disrupt. A possible mechanism mediating these effects might be found in long-term depression (LTD) in NAcc neurons caused by stimulant drugs that reduce the magnitude of LTD in NAcc shell neurons (Thomas et al. 2001) thus decreasing the postsynaptic response to glutamate (Thomas & Malenka 2003).

As discussed earlier the initiation of drug taking does not necessarily lead to drug dependence but neuroadaptations caused by the repeated exposure to drugs of abuse can modify neural substrates that in turn facilitate the development of dependence. A core feature of drug dependence is the high propensity to relapse to drug taking and drug-seeking. Several procedures have been developed to measure drug seeking and these have provided important information concerning factors that contribute to relapse.

### *Relapse and drug-seeking*

The greatest obstacle to effective rehabilitation of drug abusers is the high propensity to relapse even following extensive periods of abstinence (O'Brien 1997;

Mendelson & Mello 1996; Barrett-Larimore & Spealman 1998; Dackis & O'Brien 2001; Wallace 1989). For example, 12 month relapse rate following treatment was 50 – 90 %, depending on the study (Brandon et al. 2007; Miller et al. 1996) and was comparable across various drug classes (Brandon et al. 2007; Miller et al. 1996; Hughes et al. 2000; Medioni et al. 2005; Darke et al. 2005; Brecht et al. 2000; Rawson et al. 2000). Effective treatment therefore requires not only detoxification but also the prevention of drug seeking that eventually leads to relapse (O'Brien 2006). Neural substrates most consistently associated with relapse include the orbitofrontal cortex (OFC) and anterior cingulate cortices (ACC) and the amygdala (Childress et al., 1999; George et al., 2001; Kilts et al., 2001; Sell et al., 2000; Volkow et al., 2003). Relapse is defined as resuming the use of a drug after a period of abstinence and is usually measured as experienced drug craving, which has been shown to be critical in the cycle of relapse to drug addiction (O'Brien et al. 1998). In human subjects, the OFC and the ACC appear to be most clearly related to reported craving<sup>5</sup>. Additionally, PET imaging studies suggested that the striatum, thalamus and cerebellum to be involved in drug craving (Childress et al., 1999; Garavan et al., 2000; George et al., 2001; Hommer, 1999). In those studies, drug addicts were presented with images of drug related content (such as, videos and pictures of purchase, preparation of the drug for consumption and consumption of the drug) or were exposed to small amounts of the preferred drug (alcohol) before they had to rate the magnitude of their craving. Studies in laboratory animals have shown a remarkable concordance to clinical imaging studies regarding brain circuits mediating addictive behaviours. Although craving, the dependent variable measured in human studies, cannot be measured in animals, some models measure behaviour causally linked to craving, namely, drug-seeking.

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<sup>5</sup> Craving describes an interoceptive state that may be causally linked to behaviour eventually peaking in drug-seeking and drug-taking. It has to be noted that within the addiction literature experts are debating whether craving is indeed a primary cause of relapse (Drummond, Litten, Lowman, & Hunt, 2000; Tiffany & Carter, 1998).

Drug seeking has been measured in laboratory animals by examining the reinstatement of extinguished drug-taking that can be elicited by various stimuli, various drug exposures and stressful experiences (de Wit & Stewart, 1981; Yokel & Pickens, 1973). This procedure usually involves several training and test phases. The first phase consists of acquisition of self-administration typically in daily short-access sessions (e.g. 2 hours/day). Testing continues until drug intake is highly stable across days. Then, saline is substituted for the drug solution which usually leads to extinction of responding within a few days. Following extinction, the ability of various stimuli to reinstate extinguished behaviour is measured. Because the behaviour in this test stage is not reinforced by drug-infusions it has been considered an indication of drug-seeking. Exposure to drugs (de Wit & Stewart, 1981, 1983), environmental stimuli previously associated with self-administered drug infusions (Katner, Magalong, & Weiss, 1999; McFarland & Ettenberg, 1997; Meil & See, 1996) or stressful stimuli (Erb, Shaham, & Stewart, 1996; Shaham, 1993; Shaham, Rajabi, & Stewart, 1996; Shaham & Stewart, 1995) produce drug-seeking in this paradigm.

Drug-seeking can be seen as a behavioural marker in the transition from initial drug use to drug dependence and this transition can be tracked in various neural substrates. For example, a progression from ventral to more dorsal domains of the striatum with continued drug use has been proposed (Everitt et al., 2008). In contrast to the key role of the NAcc in the initial reinforcing properties of drugs of abuse, the dorsal part of the striatum does not seem to play a major role in the early stages of drug-taking. However, there is evidence that it becomes more important during the transition from initial use to compulsive drug-seeking and taking (Everitt et al., 2008). *In vivo* microdialysis studies have shown that cocaine self-administration increase extracellular DA in the NAcc core and shell as well as in the caudate putamen, while extracellular DA during a prolonged period of cocaine-seeking maintained by the contingent

presentation of a cocaine-associated stimulus, was only elevated in the dorsal striatum (Ito, Dalley, Howes, Robbins, & Everitt, 2000; Ito et al., 2002). Furthermore, blockade of DA receptors in the dorsal striatum markedly decreased drug-seeking, while antagonism of DA receptors in the NAcc core were without effect (Vanderschuren, Di Ciano, & Everitt, 2004). Thus, it has been suggested the transition from voluntary drug use to a habitual and eventually compulsive drug-seeking behaviour depicts a progression from ventral to more dorsal domains of the striatum (Everitt et al., 2008).

It has been suggested that these neuroadaptations facilitate the progression of drug-seeking (Everitt et al., 2008; Everitt & Robbins, 2005; O'Brien & McLellan, 1996; Tiffany, 1990) and result in diminished cognitive control (as evidenced by increased impulsivity) or hyper-responsiveness to drug-associated stimuli (Kalivas & Volkow, 2005; Volkow et al., 1993). As described earlier, stimuli associated with self-administered drugs acquire conditioned reinforcing properties that are capable of maintaining responding even in the absence of the drug (Kelley & Delfs, 1991a, 1991b). They further can initiate craving and relapse (Katner, Magalong, & Weiss, 1999; McFarland & Ettenberg, 1997; Meil & See, 1996). The acquisition of cocaine-seeking behaviour as measured using a second order schedule of reinforcement, which depends upon conditioned reinforcing properties of drug-associated stimuli, depends upon the integrity of the NAcc core and the basolateral amygdala (BLA). Lesions of these areas eliminated the acquisition of cocaine-seeking while simple drug-taking behaviour under a continuous reinforcement schedule was unaffected (Ito, Robbins, & Everitt, 2004; Whitelaw, Markou, Robbins, & Everitt, 1996). Furthermore, disconnection of these two structures by unilateral DA receptor blockade in the BLA and contralateral AMPA receptor blockade in the NAcc core greatly attenuated cocaine-seeking (Di Ciano & Everitt, 2004). The integrity of these structures and their synaptical connectivity might

be crucial for the particular strong stimulus-reward learning that enables drug-associated cues to elicit craving and relapse even after long periods of abstinence.

An important role of DAergic mechanisms in reinstatement of drug seeking has been demonstrated. Systemic administration of amphetamine, an indirect DA agonist (Schenk & Partridge 1999; de Wit & Stewart 1981), as well as selective DA<sub>2</sub>-like agonists (de Wit & Stewart 1981; Gerber & Stretch 1975; Khroyan et al. 2000; Self et al. 1996; Wise et al. 1990) and DAT inhibitors (de Vries et al. 1999) reinstated drug-seeking. On the other hand, apomorphine, a mixed DA agonist or direct D<sub>1</sub>-like agonists were ineffective (Self et al., 1996, 2000; De Vries et al., 1999; Schenk et al. 2011). Furthermore, direct D<sub>1</sub>-like agonists attenuated cocaine-induced drug seeking in rats and monkeys (Self et al., 1996, 2000; Khroyan et al., 2000) suggesting, DA<sub>1</sub> and DA<sub>2</sub>-like receptors have opposing roles in drug seeking. These negative effects of D<sub>1</sub>-like agonists seem to be specific to drug-seeking, as some maintain self-administration (Self and Stein, 1992; Weed et al., 1993; but see Caine et al., 1999b). An important role of DA in drug-seeking is further implicated since both DA<sub>1</sub> and DA<sub>2</sub>-like antagonists decreased drug seeking (Khroyan, Barrett-Larimore, Rowlett, & Spealman, 2000; Shaham & Stewart, 1996; Ettenberg, 1990, Schenk et al. 2011a).

The mesocorticolimbic DA system has been implicated as a site of these effects since infusions of AMPH, DA or cocaine directly into the NAcc or the mPFC produced drug-seeking (Stewart & Vezina 1988; Cornish & Kalivas 2000; McFarland & Kalivas 2001; Park et al. 2002). Pharmacological blockade of DA receptors in the VTA (McFarland & Kalivas 2001) and DA<sub>1</sub>-like and non-selective DA receptor antagonists (McFarland & Kalivas 2001; Capriles et al. 2002; Park et al. 2002; but see Capriles et al. 2003) also blocked cocaine-induced drug-seeking when infused into regions of the mesocortical system.

In summary, the neural mechanisms underlying drug-taking and drug-seeking both prominently involve the DAergic system. Some psychobiological traits, which have been linked to drug abuse have also been attributed to the same DA substrates mediating drug-taking and drug-seeking. For example, novelty-seeking, a core feature of sensation seeking, is mediated by the mesocorticolimbic DA system, in particular the NAcc, and has been linked to the initiation of drug-taking (Piazza et al. 1989) as cocaine-evoked DA release in the NAcc was greater in rats showing a high reactivity to novelty (Chefer et al. 2003). Furthermore, microinjection of DA antagonists into the NAcc reduced the novelty-seeking response in rats (Hooks & Kalivas 1995). It has to be noted that most of the work disentangling the mechanisms underlying drug-taking and drug-seeking has been done using cocaine, AMPH or opiates and very limited attention has been given to MDMA.

### *MDMA self-administration*

MDMA self-administration has been demonstrated in laboratory animals, including monkeys, rats and mice (Beardsley, Balster, & Harris, 1986; Braida & Sala, 2002; Cornish et al., 2003; Daniela, Brennan, Gittings, Hely, & Schenk, 2004; Daniela, Gittings, & Schenk, 2006; De La Garza, Fabrizio, & Gupta, 2007; Fantegrossi, 2007; Fantegrossi, Ullrich, Rice, Woods, & Winger, 2002; Fantegrossi et al., 2004; Lamb & Griffiths, 1987; Lile, Ross, & Nader, 2005; Ratzenboeck, Saria, Kriechbaum, & Zernig, 2001; Reveron, Maier, & Duvauchelle, 2006; Schenk, Gittings, Johnstone, & Daniela, 2003; Schenk et al., 2007; Trigo, Panayi, Soria, Maldonado, & Robledo, 2006; Wang & Woolverton, 2007). Several studies support the hypothesis that MDMA reinforced responding is greater than when saline serves as the reinforcer but is less than when the

reinforcer is either cocaine or amphetamine (Lamb & Griffiths, 1987; Lile et al., 2005; Ratzenboeck et al., 2001; Schenk et al., 2007; Wang & Woolverton, 2007). While this appears to be true during the early stages of MDMA self-administration, responding increased quite substantially when self-administration testing was extended (Schenk et al. 2003, 2007, 2008; Do & Schenk 2011).

Following the initial acquisition stage, MDMA self-administration was dose-dependent (Daniela et al., 2004; Schenk et al., 2003; Trigo et al., 2007), responding extinguished when MDMA was replaced with saline, and extinguished responding was reinstated once MDMA was available again (Daniela et al., 2006; Schenk et al., 2003). Higher doses of MDMA produced higher breakpoints (indicating greater reinforcing magnitude) under a progressive ratio schedule of reinforcement (Lile et al., 2005; Schenk et al., 2007; Wang & Woolverton, 2007) and responding was comparable to responding maintained by cocaine self-administration (Stafford, LeSage, & Glowa, 1998; Ward, Morgan, & Roberts, 2005). A number of self-administration studies have also been conducted in mice (Trigo et al. 2006), but because effects of self-administered MDMA differ markedly between mice and rats, this discussion will focus only on rats.

There is considerable variability in the latency to acquisition of MDMA self-administration and the latency is longer compared to acquisition of self-administration of other psychostimulants (Schenk et al., 2003; Schenk et al., 2007). When MDMA was available during limited access sessions (2-6 hours) the initial number of responses was relatively low (Schenk, 2009; Schenk et al., 2003; Schenk et al., 2007; Wang & Woolverton, 2007). For some rats MDMA intake escalated over days and eventually 20 – 30 mg/kg/day was self-administered during daily sessions (Colussi-Mas, Wise, Howard, & Schenk, 2010; Do & Schenk, 2011; Schenk et al., 2003; Schenk, Hely, Gittings, Lake, & Daniela, 2008; Schenk et al., 2007). The relatively low rates of MDMA self-administration has been attributed to effects on central 5HT

neurotransmission. Indeed, 5HT agonists, including MDMA (Clemens, Cornish, Hunt, & McGregor, 2006) decreased the reinforcing properties of psychostimulants (Clemens et al. 2006; Howell & Byrd, 1995; Peltier & Schenk, 1993; F. L. Smith, Yu, Smith, Leccese, & Lyness, 1986; Wee & Woolverton, 2006) and 5HT agonists are not self-administered (Gotestam & Andersson, 1975; Howell & Byrd, 1995; Tessel & Woods, 1975; Vanover, Nader, & Woolverton, 1992; Wee et al., 2005).

Because MDMA preferentially increases 5HT, it is not surprising that MDMA was not readily self-administered (Verrico, Miller, & Madras, 2007; Wang & Woolverton, 2007). With repeated daily exposure, however, 5HT neurotransmission became compromised and a sensitized DA response to MDMA in the dorsal striatum was produced (Colussi-Mas et al., 2010). Other studies support the idea that repeated exposure to MDMA sensitizes DAergic responses (Bradbury et al. 2012). Additionally, rats pretreated with MDMA acquired cocaine self-administration with a shorter latency (Fletcher, Robinson, & Slippoy, 2001) which is commonly interpreted to reflect sensitization (Horger et al. 1990, 1992; Valadez & Schenk 1994; Pierre & Vezzina 1997; Lorrain et al. 2000). Cross sensitization might also occur since MDMA self-administration was acquired with a shorter latency following experience with cocaine self-administration (Schenk et al., 2003; Schenk et al., 2007). An important role of DA in the maintenance of MDMA self-administration has been demonstrated since DA antagonists decreasing responding (Brennan, Carati, Lea, Fitzmaurice, & Schenk, 2009; Daniela et al., 2004). Because repeated exposure to MDMA produced deficits in 5HT neurotransmission (Mokler et al. 1987; Battaglia et al. 1998; Ricautre et al. 1988; Clemens et al. 2007; Schenk et al. 2007, 2011a; Do & Schenk 2011) and because 5HT is generally inhibitory to self-administration (Clemens et al. 2006; Howell & Byrd 1995; Peltier & Schenk 1993; Smith et al. 1986; Wee & Woolverton 2006) it has been



suggested that this deficit might underlie the development of higher rates of drug-taking.

Selective lesions of 5HT neurons produced by 5,7-dihydroxytryptamine (5,7-DHT) increased the firing rate of VTA DA neurons providing a potential mechanism for the development of MDMA self-administration (Guiard et al. 2008). Alternatively, the MDMA-reduced 5HT deficit may produce structural and functional changes of various 5HT receptors and other transmitter proteins (Aguirre, Frechilla, Garcia-Osta, Lasheras, & Del Rio, 1997; Bonkale & Austin, 2008; Kindlundh-Hogberg, Blomqvist, Malki, & Schioth, 2008; Kindlundh-Hogberg, Svenningsson, & Schioth, 2006; Martinez-Turrillas, Moyano, Del Rio, & Frechilla, 2006; Sexton, McEvoy, & Neumaier, 1999), which in turn may have an influence on DA neurotransmission.

#### *Reinstatement of drug seeking following MDMA self-administration*

MDMA seeking was produced by priming injections of cocaine (Schenk et al. 2008), amphetamine (McClung et al. 2010) and MDMA (Schenk et al. 2003, 2008) and MDMA injections reinstated amphetamine (Morley et al. 2004), cocaine (Schenk et al. 2008) and ethanol (Moreno-Sauz et al. 2009) seeking. An important role of both DAergic and 5HTergic mechanisms has been suggested. MDMA produced drug seeking was attenuated by DA antagonists (Schenk et al. 2011) and by the SSRI, fluoxetine (McClung et al. 2010). One extensive study evaluated the effects of various DA and 5HT agents on cue- and MDMA induced drug seeking (Schenk et al. 2011a). DA agonists generally increased (but see below) and DA antagonists decreased the drug-seeking response. Interestingly, a DA<sub>1</sub> like agonist failed to produce drug seeking, which is in line with previous findings suggesting opposing roles for DA<sub>1</sub> and DA<sub>2</sub> like receptor subtypes in cocaine-seeking (Self et al. 1996; Khroyan et al. 2000). The

reasons for this pharmacological dissociation are not clear in light of the literature on the similar behavioural effects of the D<sub>1</sub>- and D<sub>2</sub> like agonists on locomotor activity (Self et al., 1996) and cocaine reinforcement (Self & Nestler, 1995). 5HT agonists failed to alter drug seeking but the 5HT uptake inhibitor, clomipramine, decreased drug seeking (Schenk et al. 2011a). These findings are consistent with the idea that DA promotes whilst 5HT inhibits drug seeking.

Studies investigating pharmacological mechanisms of MDMA seeking are limited and more extensive work is required in order to fully elucidate the mechanisms. Since the 5HT deficit following MDMA self-administration has been shown to be dose and time-dependent (Do & Schenk, 2011), it would be interesting to test rats in MDMA reinstatement following various withdrawal periods. The shift from 5HTergic to DAergic mechanisms could be examined by measuring the 5HT and DAergic response to MDMA in drug-naïve rats and following self-administration.

### **Psychobiological traits as vulnerability markers to drug dependence**

Recently, one study developed criteria to measure three of the essential diagnostic criteria for human substance dependence (e.g., loss of control, resistance to harm or punishment, motivation for the drug) in rats that were trained to self-administer cocaine (Deroche-Gamonet et al. 2004). Interestingly, only 17% of the animals presented all three criteria, whereas 41% presented none of the criteria. This study suggested huge individual differences in the propensity to addiction. Early studies in laboratory rats demonstrated that the magnitude of reactivity in a novel environment, as indicated by locomotor responses, correlated positively with the amount of drug that was self-administered (Piazza et al. 1989). Likewise, it has recently been shown that

high trait impulsivity predisposed some animals to escalate their drug intake in the face of aversive outcomes, another key characteristic of drug dependency (Belin et al. 2008).

*Impulsivity as a vulnerability marker for drug dependence*

A wealth of studies and tests that have attempted to provide objective means of measuring impulsivity have revealed the heterogeneous and complex nature of this psychobiological trait.

Test	Dimensions	Example
Tridimensional Personality Questionnaire (TPQ)	Novelty seeking (dopaminergic system)	“acts immediately on momentary whims; extravagant spending so has difficulty saving or delay gratification”
	Harm avoidance (serotonergic system)	“lack of inhibition even when situations needs attention; overconfident and lacking in appropriate caution when dealing with unfamiliar tasks”
	Reward dependence (noradrenergic system)	“frequently quitting before maximal effort has been expended or of activities that are not immediately gratifying; lack of persistent ambition for delayed rewards”
I7	Impulsiveness	Unconscious risk taking; acting without considering dangers
	Venturesomeness	Conscious sensation seeking
Barratt Impulsiveness Scale (BIS-11)	Motor	Acting without thinking
	Attentional	Difficulties concentrating
	Non-planning	Present orientation

**Table 1.** Characteristics of the most commonly used questionnaires measuring impulsivity.

Questionnaires are commonly used in a clinical setting to chart changes on impulsivity over time. The most prevalent are the Tridimensional Personality Questionnaire (Cloninger, 1987), and the Barratt Impulsivity Scale (BIS-11; Patton et al. 1995). A summary of the main characteristics of these questionnaires is given in Table 1.

Cloninger's TQP views impulsivity as a multifaceted construct composing of three personality dimensions (Novelty seeking, Harm avoidance and Reward dependence). The TPQ is based on an assumption that these three personality dimensions reflect variations in different neurotransmitter systems (Dopaminergic, serotonergic and noradrenergic, respectively). Although the TPQ is widely used in psychiatric settings, the link between the three stipulated dimensions of the questionnaire and their respective neurotransmitter systems is still tenuous.

The Barratt Impulsiveness Scale (BIS) was developed, originally to separate impulsiveness from anxiety. The BIS is composed of three different factors: attentional impulsiveness (difficulties focussing and making quick decisions), motor impulsiveness (defined as acting without thinking) and non-planning impulsiveness (orientation in the present and not in the future) (Patton et al. 1995).

There are obvious problems with self-report questionnaires, most prominently the problem of direct questions that require the participant to assess their own cognitive abilities (e.g. attention and risk taking). Impulsive individuals will be unlikely to provide reliable insight into their impulsive attributes as they themselves perform "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and often result in undesirable outcomes" (Evenden 1999). As a result, operant tasks which are able to measure impulsive behaviour in a more objective manner are more advantageous and were, therefore, developed.

In the context of Barrett's Impulsiveness scale, impulsivity is often classified as either impulsive action or impulsive choice. Different procedures have been developed for measurement of these two separate aspects of the trait. Impulsive action is defined as the "inability to withhold from making a response" (Winstanley et al. 2006). On the other hand, impulsive choice is measured using paradigms that require a choice between small and large rewards with temporal variations, which is the basis for delay discounting procedures.

Some of these tests map favourably onto one or more of the factors of the BIS. The concept of impulsive action, or behavioural disinhibition, is best aligned with the BIS factor of motor impulsivity, and there are a number of behavioural tasks that appear to provide valid measurements of this phenomenon in both human and nonhuman subjects, including the Stop-signal reaction time task, Go/No-go task, continuous performance task and the 5-choice serial reaction time task (5-CSRTT). Tests of impulsive choice, on the other hand, appear to correspond best to non-planning domains of the BIS with delay discounting or the matching familiar figures test as examples.

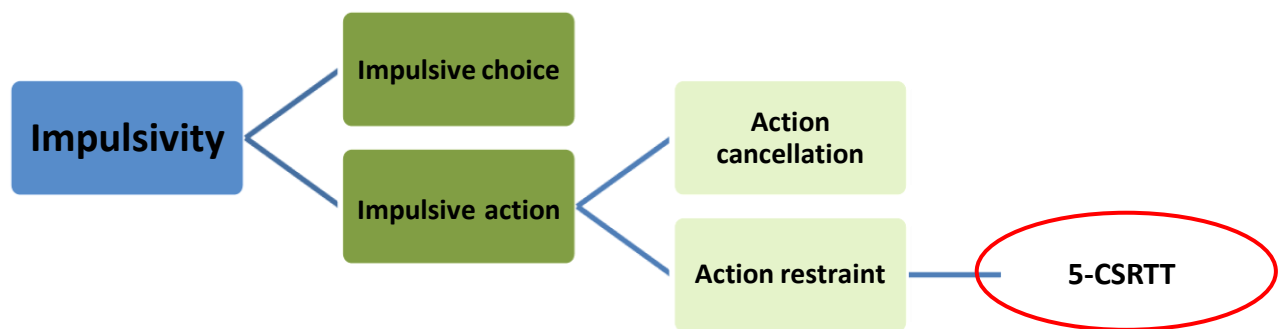
Recent evidence confirmed the independence of these two aspects of impulsivity in laboratory animals using a within subject design to compare the performance in tasks measuring both impulsive action and impulsive choice (Broos et al. 2012). In addition, pharmacological manipulations have shown dissociable effects on impulsive action and impulsive choice, suggesting independent neural circuits (Broos et al. 2012). This is not a surprising finding as all these various tasks all require behavioural inhibition at different points in the response process (e.g. choice processing, response preparation, initiation of behaviour or action cancellation) (Dalley et al. 2011). Thus, it appears only logical that impulsive action and impulsive choice can be differentiated at a behavioural as well as a neural level. Numerous studies have corroborated this by showing distinct

effects of neurochemical manipulations on different behavioural measures of impulsivity and some are summarized in Table 2 below.

	5-CSRTT	SSRT/ Go/no-go	DD	References
<b>Lesion</b>				
<b>ACC</b>	- /↑		-	Chudasama et al. 2003; Muir et al. 1996; Cardinal et al. 2006
<b>PL</b>	- /↑	-	-	Eagle and Robbins 2003; Chudasama and Muir 2001
<b>IL</b>	↑	-	-	Eagle et al. 2008; Chudasama et al. 2003;
<b>OFC</b>	↑	↑/↓	↑/↓	Eagle et al. 2008; Chudasama et al. 2003; Winstanley et al. 2004; Mobini et al. 2002
<b>NAc core</b>	- /↑	- /-	↑	Eagle and Robbins 2003; Christakou et al. 2004; Pothuizen et al. 2005; Cardinal et al. 2001
<b>NAc shell</b>	-		-	Murphy et al. 2008; Pothuizen et al. 2005
<b>Dorsal medial striatum</b>	↑	↑/?		Eagle and Robbins 2003; Rogers et al. 2001
<b>Dorso lateral striatum</b>		-		Rogers et al. 2001
<b>STN</b>	↑	- /↑	↓	Eagle & Robbins 2008; Baunez & Robbins 1997; Baunez et al. 2001; Winstanley et al. 2005; Uslaner & Robinson 2006
<b>BLA</b>			↑	Winstanley et al. 2004
<b>Manipulation</b>				
<b>DAT and D1 antagonist</b>	↑		↓	Van Gaalen et al. 2006a, 2006b;
<b>D2 antagonist</b>	-		-	Van Gaalen et al. 2006a, 2006b;
<b>5HT 1A agonist</b>	↑/↓		↑/-	Winstanley et al. 2005; 2003; Blokland et al. 2005;
<b>5HT 2A antagonist</b>	↓		-	Winstanley et al. 2003; 2004; Fletcher et al. 2007; Higgins et al. 2003; Talpos et al. 2006; Robinson et al. 2008
<b>5HT 2C antagonist</b>	↑/-		↓	Winstanley et al. 2004; Fletcher et al. 2007; Talpos et al. 2006; Robinson et al. 2008
<b>NET blocker</b>	↓	↓	↓/↑/-	Baarendse & Vanderschuren 2012; Broos et al. 2012; Robinson et al. 2008; Blondeau & Dellu-Hagendorn 2007;

**Table 2.** The effect of neurochemical manipulations on different measurements of impulsivity (↓ indicates a decrease in impulsivity ↑ indicates an increase in impulsivity - indicates no effect on the impulsivity measure).

A common paradigm used to investigate the relationship between impulsivity and drug addiction in rats, is the 5-CSRTT.



**Figure 1.** Classification of different aspects of impulsive behaviour and the 5-choice serial reaction time task (5-CSRTT).

*The 5-choice serial reaction time task (5-CSRTT)*

The 5-CSRTT was developed as a measure of both visuo-spatial attention and impulsivity. In this test, the subject is presented with a horizontal array of five apertures and is required to detect a brief visual stimulus at one aperture. Performing a response in the location of the initial visual stimulus presentation results in the delivery of a reward. At the beginning of a new trial there is a waiting period (inter-trial interval, ITI) prior to illumination of a stimulus light. During the ITI the subject must withhold from making a response so responding prior to the presentation of the visual stimulus is

defined as impulsivity. Because correct performance is dependent on both low impulsivity and intact visuo-spatial attention, however, results can be difficult to specifically attribute to one or the other of these variables. Thus, separate measures representing attention or impulsivity can be obtained in order to interpret the raw data.

### *Neural substrates of the 5-CSRTT*

The neural circuits mediating impulsivity have been well mapped in rodents and are largely consistent with data obtained from imaging studies in humans. Data from patients suffering from ADHD, Parkinson or Huntington's disease (all disorders highly associated with deficits in impulse control) suggest that the prefrontal cortex, the striatum and some structures of the basal ganglia play a role in impulse control. Many of the neural substrates mediating impulsivity are part of the mesocorticolimbic circuit which has also been implicated in drug addiction as described earlier. In particular the NAcc and the PFC seem to play key roles.

The nucleus accumbens (NAcc) is critically involved in goal-directed behavior (for a detailed review see Salamone et al. 2005) and so is a likely candidate for regulation of impulsivity. Furthermore it has been suggested to play a key role in motor performance (receiving inputs from motor structures) as well as in reward, motivation, and affective disorders (receiving its main inputs from the limbic structures, which are critical for affective processing) (Basar et al. 2010). Thus, it has been proposed that the NAcc is crucial for integrating motivational information to modulate behavior (Nestler & Carlezon, 2006). Neuroanatomically the NAcc can be divided into a core and shell region (Zaborszky et al. 1985). Each receives topographically different inputs primarily from the prefrontal cortical areas, and so the NAcc can potentially impact aspects of impulsive behaviour (for a detailed review see Basar et al. 2010).



Lesions of the NAcc core and the NAcc shell failed to alter impulsive action (Christakou et al. 2004; Murphy et al. 2008), but a functional involvement in impulsivity is clearly evident in studies combining lesions with pharmacological manipulations (Cole & Robbins, 1989). Lesions of the NAcc core attenuated impulsivity that was produced by pharmacological agents whereas lesions of the nucleus accumbens shell enhanced pharmacologically induced impulsivity (Murphy et al. 2008). Deep brain stimulation of the NAcc has also suggested different roles of the core and shell regions (Sesia et al. 2008). Because of the dense innervations the NAcc receives from the PFC, impulse control might also depend on this frontostriatal connectivity. For example, disconnection of the medial PFC/NAcc pathway increased impulsive responding in the 5-CSRTT (Christakou et al. 2001, 2004), possibly due to top-down modulation (Pezze et al. 2009). Consistent with this idea inactivation of the medial PFC produced behavioural disinhibition and concurrent electrophysiological recordings showed that this disinhibition was dependent on dopamine signalling in the NAcc shell (Ghazizadeh et al. 2012). This study suggested that, the medial PFC mediates behavioural inhibition through temporal inhibition of phasic excitations of NAcc shell neurons and an increase in the tonic firing of gating neurons (Ghazizadeh et al. 2012).

Although the involvement of the NAcc in response control, as shown by lesion studies, is not a consistent finding, evidence for a functional role is emerging. Pharmacological modulation at a striatal level and the effect of various lesions of the PFC (areas which comprise the main cortical input to the NAcc) suggest a functional role of the NAcc in the regulation of impulse control (Basar et al. 2010). Within the NAcc, DA appears to be a neurochemical of importance for impulsivity. Stimulant drugs (e.g. amphetamine and methylphenidate) that enhance synaptic DA in the NAcc

reduced impulsivity in ADHD patients (Solanto, 2002). On the contrary, amphetamine and methylphenidate enhanced impulsive action, in the 5-CSRTT (Robbins, 2002). It has been suggested that the effect of these stimulant drugs depends on initial impulsivity levels. Indeed, in animals with high baseline levels of impulsivity the effect was reversed (Puumala et al. 1996). These effects have been attributed to the DAergic effects of these drugs as administration of the selective NA reuptake inhibitor atomoxetine *decreased* impulsive responding in the 5-CSRTT (Baarendse & Vanderschuren, 2012; Fernando et al. 2012; Navarra et al. 2008; Robinson et al. 2008). In support of this idea, it has been shown that dopamine reuptake inhibitor GBR12909, also elevated impulsive action (Fernando et al. 2012, Baarendse & Vanderschuren, 2012). Thus, it has been proposed that enhanced DA neurotransmission results in increased impulsivity in the 5-CSRTT.

DA receptor blockade and DA depletion in the NAcc blocked the effects of amphetamine (Cole & Robbins, 1989; Pezze et al. 2007; Pattij et al. 2007) on impulsive action. Furthermore, D2/3 receptors seem to mediate amphetamines effects on impulsivity in particular in the NAcc core (Pattij et al. 2007; van Gaalen et al. 2006; Pezze et al. 2009; Besson et al. 2010) strengthening the key role of the DAergic mechanisms in the NAcc in impulse control.

Thus, the NAcc DA system links impulsivity and drug abuse and differential responses of the NAcc and PFC have been suggested to underlie individual differences in drug vulnerability (Morgan et al. 2002; Nader et al. 2006; Piazza et al. 1991; Tonissaaar et al. 2006). Positron emission tomography (PET) studies in nonhuman primates have shown a particular role of DA D<sub>2</sub> receptors in reflecting individual differences in intravenous cocaine self-administration was correlated with high levels of intravenous cocaine self-administration (Nader et al. 2006), a finding supported by studies of cocaine abusers (Volkow et al. 1993). In a recent study rats exhibiting high

levels of impulsivity had a low density of  $D_{2/3}$  receptors in the NAcc and also were likely to escalate their cocaine self-administration (Dalley et al. 2007a). Interestingly, in the same study, there were no differences in brain levels of DA between high and low impulsive rats suggesting the low level of  $D_{2/3}$  receptors did not reflect a presynaptic autoreceptor mechanism (which would result in elevated DA levels), but might, rather, suggest postsynaptic responses.

This finding is yet to be integrated with previous work relating high levels of DA neurotransmissions to high impulsivity. Interconnections with other brain areas and neurotransmitters might provide important information about the underlying mechanisms. In particular, the medial PFC could carry a key role as impulsivity induced by lesions of the medial PFC area was attenuated by  $D_{2/3}$  receptor antagonism in the NAcc (Pezze et al. 2009).

Some studies also implicate 5HT in impulsive behaviours. The impact of 5HT, however, appears to be opposite to that of DA. In laboratory animals, 5HT depletion via the neurotoxin, 5,7-DHT, increased impulsivity in the 5-CSRTT (Harrison et al. 1997a; Winstanley et al. 2003). Conversely, enhanced serotonin neurotransmission improved inhibitory control in this task (thus decreasing impulsive action) in transgenic rats lacking serotonin transporters (Homberg et al. 2007). Furthermore, this improved inhibitory control was also seen after administration of 5HT reuptake inhibitors in normal rats (Baarendsen & Vanderschuren, 2012).

The effects of 5HT depletion on aspects of impulsive action also appear to be region specific, as selective depletion from the mPFC, NAcc or median raphe nucleus (RN) had no effect (Fletcher et al. 2009; Harrison et al. 1997b) compared to global 5HT depletion and depletion in the dorsal RN (global: Harrison et al. 1997a; Carli and Samanin 2000; Winstanley et al. 2003; DRN: Harrison et al. 1997b). The reason for this may lie in the complexity of the 5HT system which is comprised of at least 16 different

receptor subtypes. These receptors can have both excitatory and inhibitory effects on 5HT efferents (Bubar et al. 2011). Several receptor subtypes have been linked to impulse control, but the 5HT<sub>1A</sub> and the 5HT<sub>2</sub> receptors (receptors 2a and 2c specifically) have received the bulk of the attention in studies of this nature.

The 5HT<sub>2A</sub> and 5HT<sub>2C</sub> receptors modulate DA release (Bubar et al. 2011). 5HT<sub>2A</sub> receptor antagonists decreased impulsive responding in the 5-CSRTT (Winstanley et al. 2003; Passetti et al. 2003; Winstanley et al. 2004; Talpos et al. 2006; Fletcher et al. 2007) although this effect was not produced when the antagonist was directly infused into the PFC or BLA (Carli et al. 2006; Hadamitzky & Koch 2009; Robinson et al. 2008). 5HT<sub>2C</sub> receptor antagonists, on the other hand, increased impulsive responding in the 5-CSRTT when administered systemically (Robinson et al. 2008; Winstanley et al. 2004; DRL: Higgins et al. 2003) as well as intra NAcc (Fletcher et al. 2007; Robinson et al. 2008), although there was no effect following intra prelimbic (PL) or infralimbic (IL) microinjection (Robinson et al. 2008). 5HT<sub>2C</sub> agonists decreased impulsive responding (Navarra et al. 2008). The failure of pharmacological manipulation of 5HT receptors in the PFC to alter impulsivity (Winstanley et al. 2003; Robinson et al. 2008; Hadamitzky & Koch, 2009) coupled with effects when administered into the NAcc (Fletcher et al. 2007; Robinson et al. 2008) supports the idea of a differential role of these two sites in impulsivity (Robinson et al. 2008). However, the PFC might also play a role. There is evidence that impulsivity is related to *increased* 5HT levels in the frontocortical regions. Increased 5HT utilization in the right frontal cortex was correlated with impulsivity levels (Puumala & Sirvio, 1998). This finding is supported by an *in vivo* microdialysis study which showed that 5HT levels in the PFC were positively correlated with impulsive responding (Dalley et al. 2002). The reasons for this are currently unknown and further research is required to

elucidate the relationship between 5HT and impulsive responding in relation to specific serotonin receptors in specific brain regions.

Complex interactions between the 5HT and DA have been suggested to contribute to the expression of impulsive behaviour and account for some of the contradictory findings in this area of research. The D<sub>1</sub>-antagonist, SCH23390, blocked the effects of global 5HT lesions on impulsivity, whereas 5HT depletion attenuated the effects of amphetamine in the 5-CSRTT (Harrison et al. 1997a). If increased DA neurotransmission results in higher impulsivity, then this might explain the findings that both 5HT<sub>2C</sub> antagonists and DA agonists increased premature responding (Fletcher et al. 2007; Winstanley et al. 2004; Higgins et al. 2003; Dalley et al. 2011; van Gaalen et al. 2006).

Cocaine-dependent outpatients (Coffey et al., 2003; Moeller et al., 2004) and young stimulant users (Leland and Paulus, 2005) were more impulsive as indicated by self-report measures (typically the BIS). Moreover, higher impulsivity in stimulant users was correlated with higher polysubstance involvement (McCown, 1988; Semple et al., 2005), binge use (Semple et al., 2005), and poorer treatment outcomes, including lower retention levels and higher dropout rates (Moeller et al., 2001; Patkar et al., 2004; Streeter et al., 2007). Studies in humans cannot, however, determine whether impulsivity precedes the initiation of drug use or is a consequence of chronic exposure to drugs (Bolla et al. 1999; Hester & Garavan 2004). Animal studies allow for the examination of impulsivity prior to and after extensive exposure to drugs of abuse. Furthermore, individual differences in the tendency to acquire drug self-administration can easily be observed in the laboratory rat (e.g. Deminiere et al. 1989, Schenk et al., 2007).

In laboratory animals, there is considerable variability in both impulsivity and self-administration. Chronic exposure to psychostimulant drugs may lead to long-term neuroadaptations that produce deficits in impulse control in rats (Paine et al. 2003; Dalley et al. 2005 a,b; 2007b). Differences in the propensity for these changes to occur might also account for individual differences in vulnerability to dependence to different drugs (Koob et al. 1998). These possibilities have been studied in laboratory animals by measuring both impulsivity and drug self-administration.

Using the 5CSRTT impulsivity has been measured as the inability to withhold a premature response for a set time period, suggesting an inability to exert inhibitory cognitive control (Bari, Dalley & Robbins, 2008). Rats classified as high impulsive (HI) in this task also demonstrated several indices of drug dependence. Cocaine intake increased over days (Dalley et al., 2007), break points under progressive ratio schedules were higher and there was persistent drug seeking even when responding was punished by electric foot shocks (Belin et al., 2008). Reinstatement of cocaine self-administration was more pronounced for HI rats (Economidou et al. 2009), suggesting a predisposition to relapse. Initial measures of impulsivity did not, however, correlate with the initial sensitivity to drugs of abuse (e.g Dalley et al. 2007a). Rather, the latency to acquisition of drug self-administration was related to the locomotor response when placed in a novel environment, a sensation-seeking phenotype (Piazza et al. 1989). Indeed, Belin et al. (2008), showed an association between both the response to novelty and the acquisition of cocaine self-administration *and* between high impulsivity and the escalation of cocaine intake that occurs with repeated self-administration in some subjects.

### *Novelty-seeking*

The interest and need for novel stimuli has been suggested to be biologically determined, as our sensory systems are designed such that stimuli lose their impact with repeated or constant presentation. Thus, organisms will more readily attend to novel information than familiar information (Bardo, Donohew, & Harrington, 1996). It is well established that novel stimuli will increase levels of arousal. In humans this can be measured by electrodermal activity and this arousal pattern is similar to that seen with psychostimulant drugs, like caffeine (Davidson & Smith, 1991). The seeking of novelty in humans can also be measured using various personality scales, the most prominent being Zuckerman's Sensation Seeking Scale and Cloninger's Novelty Seeking Scale. Zuckerman's Sensation Seeking Scale consists of four subscales which are summarized in Table 3.

Subscale	Content
Thrill and adventure seeking	Engagement in physically risky activities which provide unusual situations and novel experiences
Experience seeking	The need for a non-conforming lifestyle, travel, music, art, drug-taking and unconventional friends
Disinhibition	The need for social stimulation like parties, social drinking, sex with a variety of partners
Boredom Susceptibility	Aversion to boredom produced by a lack of variety in conditions or persons

**Table 3.** Zuckerman's Sensation Seeking Scale subscales

The questionnaire consists of 40 pairs of statements (one high and the other low in their sensation value) with 10 items per subscale.

A number of studies support the idea that individuals high in sensation seeking might be particularly susceptible to drug abuse (Kelly et al. 2006; Semple et al. 2005; Moeller et al. 2001; Martin et al. 2002; Ball et al. 1994) and individuals who scored high on sensation seeking scales were more likely to experiment with various illicit drugs (Martin et al. 2002; 2004). More importantly, subjects who scored high on a sensation seeking scale were more responsive to some drugs of abuse as measured by various scales of the ARCI, POMS and VAS that measure positive subjective effects (Hutchison et al., 1999; Stoops et al., 2007; Kelley et al., 2006; 2009; but see Corr and Kumari, 2000) and also demonstrated greater incentive motivation to self-administer amphetamine in a laboratory setting (Stoops et al., 2007). Furthermore, some studies suggested a predictive role of sensation-seeking for adolescent onset of ecstasy use (Wu et al. 2010; Martins et al. 2008) and MDMA users displayed significantly higher scores in a sensation-seeking scale than non-users (Gerra et al. 1998). Novelty seeking, as a core feature of sensation seeking, has been shown to predict likelihood of substance abuse (Cloninger, 1987) and early onset of alcohol abuse (Howard et al. 1997).

In laboratory animals, sensation-seeking has been operationalized as the response to novelty and this response varies considerably within groups of rats (see Blanchard et al., 2009 for review). Animal studies have also suggested a role of these traits in drug self-administration. The idea that the response to novelty by rat subjects might predict initial response to the positively reinforcing effects of drugs of abuse is based on the hypothesis that this response reflects the trait of sensation seeking in humans. To test the relationship of behavioural traits to drug taking behaviour, sensation-seeking has been modelled in animals by their response to a novel environment first described by Piazza et al. (1989).



### *Reactivity to a novel environment (locomotor activity)*

Piazza et al. (1989) developed a measurement to investigate reactivity to a novel environment in rats. Animals were exposed to test chambers equipped with photo beams to measure locomotor activity during a 120 min session. Subsequently animals were divided into two subgroups (high responders (HR), and low responders (LR)) based on a median split of the locomotor response (Piazza et al., 1998). It is difficult to attribute high levels of locomotor activity of a rat to sensation seeking but several aspects of this response are consistent with this trait. For example, locomotor responses in a novel environment predicted a preference for a novel over a familiar environment. Rats which showed high levels of locomotor activity in a novel environment explored an open, illuminated compartment with shorter latency and for a longer time period. This behaviour indicates a resemblance to the concept of sensation seeking in humans as defined by Zuckerman (1984) "...the need for varied, novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experiences". Thus, some animals show increased locomotor activity in novel environments which they do not exhibit in familiar environments (Dellu et al. 1996).

A link between novelty seeking and drug dependence has been suggested since HR acquired self-administration of low doses of amphetamine and cocaine more rapidly (Piazza et al., 1989; 2000; Pierre & Vezina 1997; Deroche-Garmonet et al. 2004; Belin et al. 2008; Beckmann et al. 2011) suggesting that, like human subjects, they are more sensitive to the initial positively reinforcing effects of these drugs. Higher rates of responding have also been observed for self-administration of other drugs of abuse, such as morphine and ethanol (Nadal et al. 2002; Ambrosio et al. 1995). These findings form the basis of considering HRs as a vulnerable phenotype relevant to the development of drug addiction.

This concordance between novelty seeking and acquisition of self-administration might reflect the variability in the response of a common neural substrate. Indeed, it has been suggested that the response to a novel environment (Bardo et al. 1996) and the acute positively reinforcing effect of drugs of abuse (Koob et al. 1998; Nestler, 2005) are both mediated by activation of the mesolimbic DA system. Thus, it has been proposed that the different response to novelty seeking represents responses of the mesolimbic DA system that is also reflected in different responses to drugs of abuse (Piazza et al. 2000). According to this rationale, the high novelty seekers are those that are particularly sensitive to activation of the mesolimbic DA system by both exposure to novelty and drugs of abuse.

Indeed, extensive DA depletion caused by neurotoxic lesions of the anterolateral region of the hypothalamus reduced locomotor and rearing behaviour in a novel open field and this effect was blocked by administration of the DA agonist, apomorphine (Fink & Smith, 1980). Novelty-seeking was also blocked by microinjection of DA antagonists directly into the NAcc (Hooks & Kalivas, 1995) as well as by systemic administration (Bardo et al. 1989, 1993; Misslin et al. 1984). Microdialysis showed a novelty-induced increase in extracellular levels of DA in the NAcc (Saigusa et al. 1999) and basal DA uptake and release were reduced in animals high in novelty-seeking. Following a cocaine injection there was an increased DA response and an enhanced locomotor response to cocaine which was of greater magnitude in HR rats (Chefer et al. 2003).

#### *Aims of the current project*

There is considerable variability in the latency to acquisition of MDMA self-administration (Schenk 2009; Schenk et al. 2012) as well as in the magnitude of the drug-seeking response produced by exposure to various drug primes (Schenk et al., 2008; Schenk, Gittings and Colussi-Mas 2011). The present study, therefore, determined whether the variability could be explained by differences in impulsivity and/or sensation seeking, as measured by the 5-CSRTT and the locomotor response to a novel environment.

Impulsivity has also been suggested to predict early onset of substance abuse disorders in general (Tarter et al. 2003), as well as first ecstasy use (Schilt et al. 2009). Impulsivity has been measured in laboratory animals through the use of the 5-choice serial reaction time task (5-CSRTT) (Bari, Dalley and Robbins 2008; Robbins, 2002). In this paradigm, the rat is presented with a horizontal array of five apertures and is required to detect a brief visual stimulus at one aperture. Performing a nose-poke response at the correct location results in the delivery of a reward. Impulsivity, defined as the inability to withhold from making a motor response (Winstanley et al. 2010), is operationalized as premature responses. A large body of literature shows that performance on the 5-CSRTT depends on the functional integrity of the same limbic-cortical-striatal brain structures involved in chronic drug abuse (as reviewed by Robbins, 2002). Furthermore, serotonin (5HT) and dopamine (DA) lesions produced distinct deficits on the 5-CSRTT. Specifically, selective 5HT depletion increased impulsivity (Harrison, Everitt, Robbins, 1997a; Winstanley et al. 2004). MDMA self-administration produced time and dose dependent 5HT deficits (Do & Schenk, 2011; Colussi-Mas et al. 2010), and so MDMA self-administration might be expected to increase impulsivity and the risk to relapse as measured by drug-seeking.

## **II. General Methods**

(The following methods have partly been published in Bird and Schenk (2012). Contribution of impulsivity and novelty-seeking to the acquisition and maintenance of MDMA self-administration. *Addiction Biology*, doi: 10.1111/j.1369-1600.2012.00477.x. [Epub ahead of print])

### **Subjects**

Male Sprague-Dawley rats (n=144) weighing 180g-200g at the beginning of the study were bred in the vivarium at Victoria University of Wellington. The vivarium was temperature (19-21°C) and humidity (55%) controlled and was maintained on a 12-h light/dark cycle (lights on at 0700 h). They were initially housed in groups of four and then in pairs during acquisition of the 5-CSRTT. During training of the 5-CSRTT, the rats were food-restricted but had free access to water while in their home cage. Two hours after the daily training session rats received food (~ 5 g of food per 100 g body weight) to maintain them at 85-90% of their free-feeding weights. Weights were recorded 3 times per week and the amount of food was adjusted to maintain the weights according to the normal growth curve. Once tests of impulsivity were completed, rats were separated and housed individually in standard polycarbonate cages with food and water available *ad libitum*. Self-administration tests were conducted during the light portion of the cycle except for the 6 hr tests of drug-seeking that began during the light portion but were completed during the first hour of the dark portion of the cycle.

All experimental procedures were approved by the Animal Ethics committee at Victoria University of Wellington.

## **Surgery**

A siliastic catheter (Dow Corning, Midland, MI, USA) was implanted in the external jugular vein under deep anesthesia produced by a combination of ketamine (90.0 mg/kg, IP) and xylazine (9.0 mg/kg, IP). The external jugular vein was isolated and the tubing was inserted and fixed in place. The distal end of the tubing was passed subcutaneously to an exposed portion of the skull and fitted onto a piece of 22 ga stainless steel tubing which was then secured to the skull using jeweller's screws embedded in acrylic dental cement. Carprofen (5.0 mg/ml, s.c.) was administered at 0, 24, and 48 hours following surgery. Compound sodium lactate (10 ml, s.c.) was administered immediately after the surgical procedure. Each day following surgery the catheters were infused with 0.2 ml of a sterile saline solution containing heparin (3.0 IU/ml) and penicillin G potassium (250 000 IU/ml) to maintain catheter patency, and to prevent infection and the formation of clots. There were at least 6 days of recovery before any other test procedures were conducted.

## **Behavioural Apparatus**

### *Self-administration*

Self-administration testing was conducted in 31 standard operant chambers (Med Associates, ENV-001) equipped with two levers and a light stimulus. Depression of the right ("active") lever resulted in an automatic infusion of drug solution (100 µl delivered over 12 sec) and the 12 sec illumination of a stimulus light located above the active lever. Depression of the left ('inactive') lever had no programmed consequence. The exposed stainless steel tubing was attached to a length of microbore tubing that was

connected through a swivel apparatus to a 20-mL syringe housed in a mechanical pump (Razel, Model A with 1 rpm motor).

#### *Reactivity to novelty*

Locomotor activity in a novel environment was measured 6 days following implantation of the intravenous cannula. The data from one rat were excluded due to technical difficulties with one of the chambers. Horizontal locomotor activity was measured in 16 plexiglas chambers (Med Associates Inc, USA; model ENV-515 measuring 42 x 42 x 30cm) enclosed in sound-attenuating boxes. Each chamber was equipped with four sets of sixteen infra-red sensors spaced evenly along the sides of each box producing a lattice of beams and creating squares of dimension 25mm x 25mm. The sequential interruption of a group of three beams, which was the approximate size of the body of the rat, was recorded as one activity count. Activity scores were obtained during a single 120 min session.

#### *5-CSRTT*

The apparatus consisted of 4 nine-hole chambers (Med Associate Inc, USA, NPW-9L, measuring 25 x 25 x 25 cm) each housed within a wooden sound-attenuating box. The left wall of the chamber was curved and equipped with nine contiguous apertures (2.5 x 2.5 x 2.5 cm) set 2 cm above the grid floor. Each aperture was fitted with a yellow light emitting diode (LED) and an infrared detector (1.0 cm from the front of the aperture). The opposite wall contained a food magazine equipped with a dipper (0.01 ml). A light (1.0 cm in diameter) was fitted above the food magazine (6.0 cm from the ceiling). Only the five central holes (holes 3, 4, 5, 6, 7) were used during the task (Figure 2).

## **Experimental procedures**

### *5-CSRTT*

#### **Habituation**

Initially, the animals were habituated to the operant box, feeding regimen, and response apertures prior to training and testing. During two 20 min sessions non contingent reward from the food magazine and the five response apertures was provided. All lights were off during these two sessions.

#### **Magazine training (Autoshape I)**

Initial shaping consisted of magazine training, during which the reinforcer was delivered non contingently every 15 s for 20 min. After 2-5 consecutive sessions all the free reward was consumed within a session, and a fixed interval schedule of reinforcement was imposed with responses reinforced according to the Autoshape protocol described below.

#### **Nose poke training (Autoshape II and III)**

This training stage initially consisted of only one stage (Autoshape III) during which one randomly determined hole was illuminated for 15 min at a time until a nose poke was produced in the illuminated hole. Responses in other holes had no programmed consequence. The stimulus light was presented randomly an equal number of times in each of the five holes. During preliminary experiments it became apparent

AUTOSHAPING		Stimulus duration (s)	ITI (s)	LH (s)	Criterion to move to next stage	description
Stage I		15			5 days	Five lights on for 15 s and response in any of these holes gives a reward. After 15 s without responding, a free reward is presented. After 10 correct trials no free reward is presented anymore.
Stage II		∞			100 correct trials	Five lights on (no time limit) and response in any of these holes gives a reward. No free reward is presented.
Stage III		15 min			≥50 correct trials	One hole illuminates at a time at a random location until the rat responds in the lit hole. After 15 min without correct response a free reward is presented. Responses in other holes have no programmed consequence. The stimulus light was presented randomly an equal number of times in each of the five holes.
5-CSRTT	training stage	stimulus duration (s)	ITI (s)	LH (s)	Criterion to move to next stage	description
	1	30	2	30	≥30 correct trials	One hole illuminates at a random location for 30 s. If the rat makes a response a reward is presented. After an ITI of 2 s the house light goes off and a new trial is automatically initiated. Response errors (omission, commission, premature response) are punished by a 5-s time-out period where lights are off and no action can be performed.
	2	20	2	20	≥30 correct trials	Same as above but stimulus duration and limited hold (LH) are slowly decreased while the ITI is slowly increased.
	3	10	5	10	≥50 correct trials	
	4	5	5	5	≥50 correct trials >80% accuracy	
	5	2.5	5	5	≥50 correct trials >80% accuracy <20% omission	
	6	1.25	5	5	≥50 correct trials >80% accuracy <20% omission	



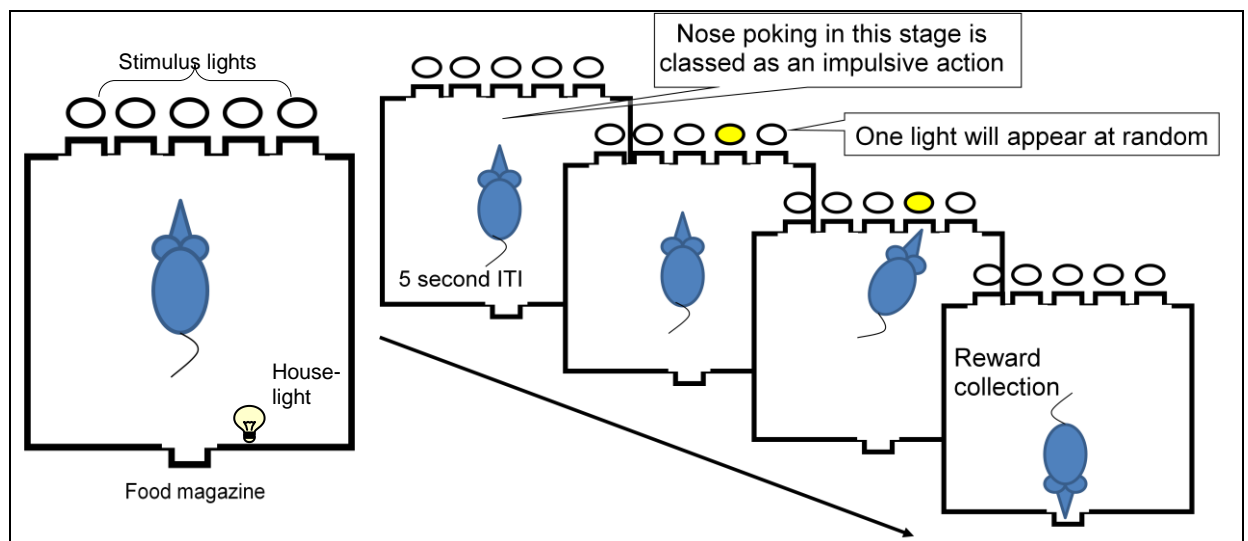
5-CSRTT	training stage	stimulus duration (s)	ITI (s)	LH (s)	Criterion to move to next stage	description
	7	1	5	5	≥50 correct trials >80% accuracy <20% omission	
	8	0.9	5	5	≥50 correct trials >80% accuracy <20% omission	
	9	0.8	5	5	≥50 correct trials >80% accuracy <20% omission	
	10	0.7	5	5	≥50 correct trials >80% accuracy <20% omission	
	11	0.6	5	5	≥50 correct trials >80% accuracy <20% omission	
	12	0.5	5	5	≥50 correct trials >80% accuracy <20% omission	

**Table 2.** Adapted training protocol for the 5-CSRTT. Habituation and autoshaping usually took 2 weeks before the actual 5-CSRTT training started. ITI, inter-trial interval; LH, limited hold.

that an additional training step (Autoshape II) was required to produce more rapid acquisition of the nose poke response. For this procedure, all stimulus light were illuminated until a nose poke response made in any of the holes was reinforced.

## 5-CSRTT

Training was conducted during 30 – 40 daily sessions (5-6 days per week) according to a training protocol described by Bari et al (2008), with slight modifications. Each session continued for 100 trials or 45 min, whichever occurred first. Following habituation and autoshaping, the procedure was modified so that only nose pokes in the hole in which the LED was illuminated were reinforced.



**Figure 2.** Schematic diagram of the 5-choice serial reaction time task (5-CSRTT) chamber and a possible trial sequence. Every trial starts with a 5 second waiting period (intertrial interval, ITI) where the rat has to scan the five apertures for the appearance of the light stimulus and respond in the correct aperture in order to earn a reward. If the rat responds during this ITI (premature response) or at an incorrect aperture (incorrect response) a 5 second time-out period is introduced where all lights are extinguished and no reward is provided.

The session began with the illumination of one of the five apertures which varied randomly across trials. Responding was reinforced with a dipper of sweetened condensed milk if a nose-poke into the correct location was produced. Failure to respond within 5 s of the onset of the light stimulus (“omission”) resulted in a brief time-out period (5 s), during which all lights were extinguished. Nose pokes made into the wrong location (“error responses”) or made before the onset of the LED stimulus (“premature responses”) were also followed by a 5 s time-out period. After each trial ended (e.g. time-out or the presentation of a reward) the house light was illuminated for a 5 sec period after which another aperture was randomly illuminated.

Four measures were obtained: (1) number of correct responses, (2) premature responses, (3) error responses, and (4) number of omissions. These 4 measures produced three dependent variables; (1) choice accuracy [(correct responses/total number of responses)\*100], (2) impulsivity [(premature responses/number of trials)\*100], and (3) omission rate [(number of omissions/number of trials)\*100]. Stable performance was defined as greater than 65% accuracy and less than 35% omission rate during 3 consecutive baseline days. Rats that failed to reach this criterion within 40 daily sessions were excluded from further testing. Once the stability criteria were met, tests to provide a baseline score of impulsivity for the remaining rats were conducted during 5 daily sessions.

#### Milk exposure vs. water exposure

A number of studies from our laboratory have indicated that about 50% of the rats meet the criterion for acquisition of MDMA self-administration (Schenk et al. 2003, 2007; Colussi-Mas et al. 2010; Do and Schenk 2011). Curiously, the present protocol yielded a much high percentage and 81 % met the criterion. This finding suggested that

some aspects of the procedure might have increased the initial response to the reinforcing effects of MDMA. Two possible explanations are an effect of handling due to the long training period, or a possible learning effect from the training and the exposure to sweetened condensed milk. To assess whether the exposure to sweetened condensed milk alone influenced the latency to acquisition of MDMA self-administration a subgroup of rats were introduced to the nine-hole-chambers where they either received sweetened condensed milk or water. The 35 daily sessions lasted for 25 minutes and were conducted 5-6 days a week. The sweetened condensed milk or water was delivered non contingently every 15 seconds. The total amount of sweetened condensed milk delivered was the same as the amount of 100 possible reinforced trials available in the original task of the 5-CSRTT.

#### *Acquisition of MDMA self-administration*

Acquisition of self-administration proceeded during daily 2 hr tests conducted 6 days per week. On the seventh day of each week, cannula patency was verified by an immediate loss of the righting reflex following administration of 0.15 ml of sodium pentobarbital (50.0 mg/ml, i.v.).

Active lever responding was initially reinforced by an infusion of 1.0 mg/kg/infusion MDMA and each lever response was reinforced by an infusion of MDMA (Fixed ratio 1 schedule; FR-1). Once 90 infusions of this dose of MDMA had been self-administered, the dose was reduced to 0.5 mg/kg/infusion and testing continued until 150 infusions had been self administered, as in our previous studies (Colussi-Mas et al. 2010; Schenk et al. 2007; Do & Schenk, 2011). Rats that failed to self-administer the initial 90 infusions within 25 daily sessions, were excluded from

further testing. A control group that was yoked to MDMA self-administering rats received infusions of the heparin/saline vehicle.

#### *Acquisition of cocaine self-administration*

Cocaine self-administration was conducted in a manner similar to MDMA self-administration during daily 2 hr sessions, 6 days per week. On the seventh day of each week, cannula patency was verified by an immediate loss of the righting reflex following administration of 0.15 ml of sodium pentobarbital (50.0 mg/ml, i.v.).

Active lever responding was reinforced by an infusion of 0.25 mg/kg/infusion cocaine. A 99% confidence interval was placed around the normalized mean number of responses on the inactive lever on each test session and the first day that the number of active lever responses was higher than the upper tail of this interval, and remained so for the subsequent test sessions, was considered the day to acquisition of cocaine self-administration (Horger et al. 1991; Horger et al. 1992).

#### *Drug-seeking*

Drug seeking was assessed during a recurring set of tests comprised of 3 phases. Phase 1 consisted of at least 2 days of responding maintained by 0.5 mg/kg MDMA and the illumination of the drug-associated light stimulus (FR 5 schedule). During phase 2 the drug solution was replaced with vehicle (3 IU heparinised saline) and the light stimulus was omitted. This phase of testing continued until fewer than 30 lever responses were produced. At the start of phase 3, MDMA (0.0, 5.0 and 10.0 mg/kg, IP) was administered and responding maintained by vehicle and the light stimulus was

recorded, as per our previous studies (Schenk et al. 2008; Schenk et al. 2011a). All rats received all doses of MDMA administered in random order.

### **Experimental protocols**

Of the sample of 144 rats, 104 were trained in the 5-CSRTT, tested for novelty responses and subsequently tested for the acquisition and/or maintenance of MDMA self-administration (Table 4). A separate group (n=16) was screened for novelty-seeking only and subsequently tested for acquisition of cocaine self-administration. A final group (n=24) was used to further investigate the basis for the high acquisition rate we observed throughout these particular experiments.


Because there were only 4 nine-hole chambers, the 104 rats that were trained to perform the 5-CSRTT were run in groups of 16 or 40 (groups 1-4: 16 rats each; group 5: 40 rats). Testing took place over a period of 12 months. Of the initial 104 rats, 46 acquired the 5-CSRTT within the 40 day cut-off period. One rat died from the anaesthesia leaving 45 rats for self-administration tests. In order to determine the effects of MDMA self-administration on impulsivity, 16 rats were matched according to their impulsivity scores prior to self-administration. One rat of each pair self-administered MDMA, and the other saline leaving 37 rats that proceeded to MDMA self-administration. Thus, of the 45 rats, 37 self-administered MDMA and 8 were yoked and received saline according to the self-administration response of an MDMA partner.

All 37 rats were initially trained to self-administer but 3 rats died and 8 rats did not meet acquisition criterion. One of the rats that died was yoked to a control rat and for the remaining test sessions this control rat was yoked to another MDMA rat. Some of the rats (n=8) were not tested beyond acquisition of MDMA self-administration and the other rats were tested either for drug-seeking (n=11) or impulsivity (7 MDMA and 8

vehicle rats). The impulsivity tests began 24 hours following the last self-administration session and continued for 20 consecutive days.

		<i>Self-administration</i>						
Group	N	5-CSRTT acquired	Novelty seeking	<i>acquired</i>	<i>not acquired</i>	Drug- seeking	5-CSRTT posttest	Excursus
1	16							
2	16							
3	16	7	6**	6	1	6		
4	16	3	3	1	2	1		
5	16	9*	8	4†	2	4		
6	20	11	11	9	2			
7	40	16		6†	1		15	
8	16		16	13 (coc)				
9	24							24

\* one rat died from anathesia; † 3 rats lost catheter patency; \*\* one box failure

<i>Time course</i> 						
Experiment	<i>Setting up 5-CSRTT</i>	<i>Acquisition MDMA SA</i>	<i>Drug- seeking</i>	<i>5-CSRTT Posttest</i>	<i>Acquisition Cocaine SA</i>	<i>Excursus</i>
Group	1-2	3-7	3-5	7	8	9
n	32	104	44	40	16	24

**Table 4.** Overview over experimental protocols.

For drug-seeking tests the reinforcement schedule was increased to FR 5 and the session length was increased to 6 hours. Following at least 7 days, tests of drug-seeking began. Cannula patency failed for 4 of the rats before all of these data could be collected leaving a final sample size of 7.

## Drugs

Racemic MDMA-HCl (ESR, Porirua, New Zealand) and cocaine HCl (Merck, Germany) were dissolved in a sterile solution of 3 IU heparinized saline for self-administration and MDMA-HCl was dissolved in 0.9% saline for intraperitoneal injections. Intravenous infusions were in a volume of 100  $\mu$ l and intraperitoneal injections were in a volume of 1.0 ml/kg. All drug doses were calculated based on salt weights.

## Data analysis

The relationship between impulsivity or novelty-seeking and (a) acquisition of MDMA or cocaine self-administration, measured as the number of days required to self-administer the initial 90 infusions of 1.0 mg/kg MDMA or the total 240 infusions, and (b) drug-seeking behaviour, as measured by active lever responses following different priming doses was analysed by linear regression (Pearson). For drug seeking tests the number of responses produced during Phases 1 and 2 was compared using paired *t* tests and responses as a function of MDMA dose during Phase 3 were analysed using a two-way repeated measures ANOVA (lever x dose). To analyse changes in performance in the 5-CSRTT following MDMA self-administration the data was summarized in 5 day bins and separate repeated measures ANOVA were used (MDMA/saline vs. session) on each of the dependent measures (accuracy, omission, premature responses).

To compare the latency to acquisition to MDMA self-administration experimental groups were compared using the  $\chi^2$ -test. All analyses were conducted using SPSS statistical packages (SPSS Inc; version 18.0 for Windows 2007). For all tests the level of significance was set at  $p < 0.05$ .



### **III. Results**

#### **Chapter 1: Establishing parameters for the 5-CSRTT**

##### *Overview*

The 5-CSRTT is a valuable tool for assessing impulsivity and cognitive functioning. It has been successfully used to measure discrete and somewhat independent variables of behavioural control in rats and in mice. In order to successfully use the 5-CSRTT, however, some adaptations may be required to cater for differences in cognitive capabilities or visual acuity of various species and strains. For example, it may be necessary to adapt the characteristics of training (such as training or session length), testing procedure (such as final testing parameters) and equipment (such as brightness of the light stimulus). Previous findings have shown that Sprague-Dawley (SD) rats are capable of learning the 5CSRTT, but they require more training sessions compared to Lister hooded rats (e.g., Carli et al. 1983; Cole & Robbins 1989; McGaughy et al. 2002). Furthermore, in one study SD rats were unable to reach the performance criteria stipulated by many laboratories (80% accuracy, 15% omissions) despite extensive training (Paine et al 2007).

The experimental chambers within our laboratory differed slightly from the standard set-up for the 5-CSRTT. Firstly, the chambers were not equipped with a food pellet dispenser. Instead a liquid dipper delivered 0.01 ml of the reinforcer. Secondly, the chambers were not equipped with an infra-red photo beam in the food magazine so that we were unable to record whether the reward was collected, which typically would

be the trigger to initiate a new trial. The program automatically initiated a new trial after a certain period of time during which the reward was presented (7 s). The measure most likely affected by this modification would be rate of omission as a new trial always started automatically regardless of whether a response was produced or not. To date there are no studies describing variations like this in the 5-CSRTT, although at least one study indicated that the automatic initiation of new trials increased the number of omitted trials without having an effect on other measures (Semenova et al. 2007).

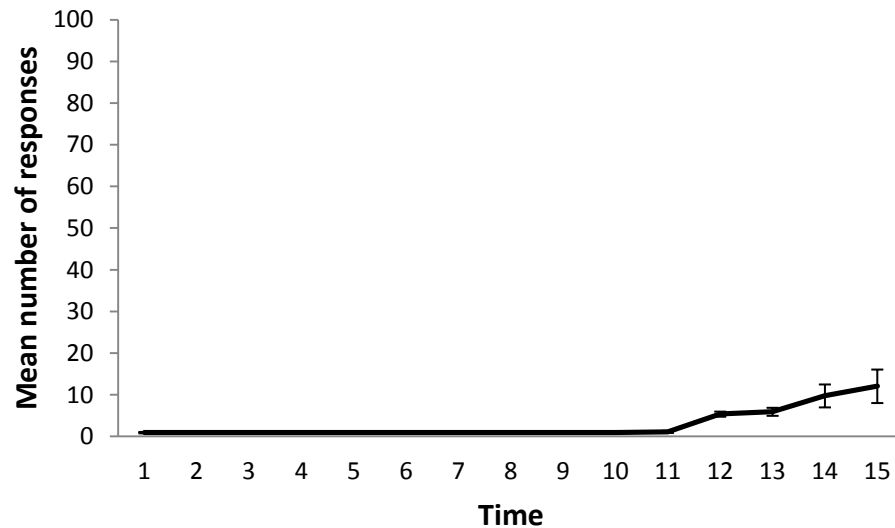
A 0.8% saccharin solution was initially used as reward, as this dose has previously been shown to reliably reinforce self-administration behaviour (Schenk, 2000). Two groups of rats (total  $n = 32$ ) were used to establish test parameters and training procedures.

In order to establish training and testing criteria, 2 groups of rats were trained consecutively. The latency to learn the nose poke behaviour (number of sessions) and the rate of responding (number of responses) were measured as dependent variables. Table 3 ( in II. General methods) gives an overview of the various stages of training used for this preliminary study.

## *Results*

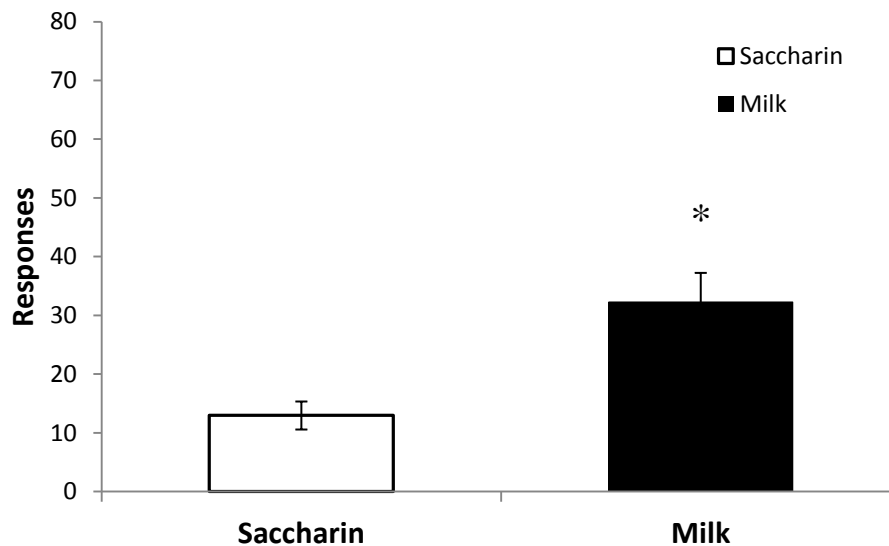
### **Group 1**

Following habituation to the test chambers and the saccharin solution, a first group of 16 rats was trained to perform the nose poke response (Autoshape Stage I). Figure 3 shows minimal performance during the first 2 weeks.



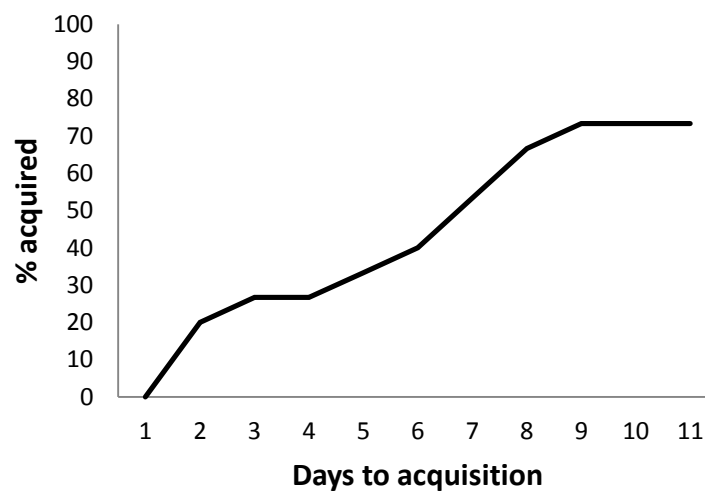
**Figure 3.** Responding reinforced by 0.8% saccharin solution during the first 15 days of training. There was slight increase in the number of responses in the last four days of testing.

Since the saccharin did not appear to reinforce responding to an adequate extent, the reinforcer was changed to sweetened condensed milk. Animals were habituated to sweetened condensed milk before any further training. To prevent hyponeophagia a sample of sweetened condensed milk was placed in the home cage and left over night for three consecutive days. Indeed, Student's T-test revealed that responding increased significantly as soon as sweetened condensed milk was substituted for saccharin (Figure 4,  $t = -4.232$ ,  $df = 15$ ,  $p < 0.01$ ).



**Figure 4.** Mean number of responses for group 1 (n=16) on the last three days of saccharin versus the first three days on sweetened condensed milk reinforcement. Responding reinforced by sweet milk is significantly higher ( $p < 0.01$ ).

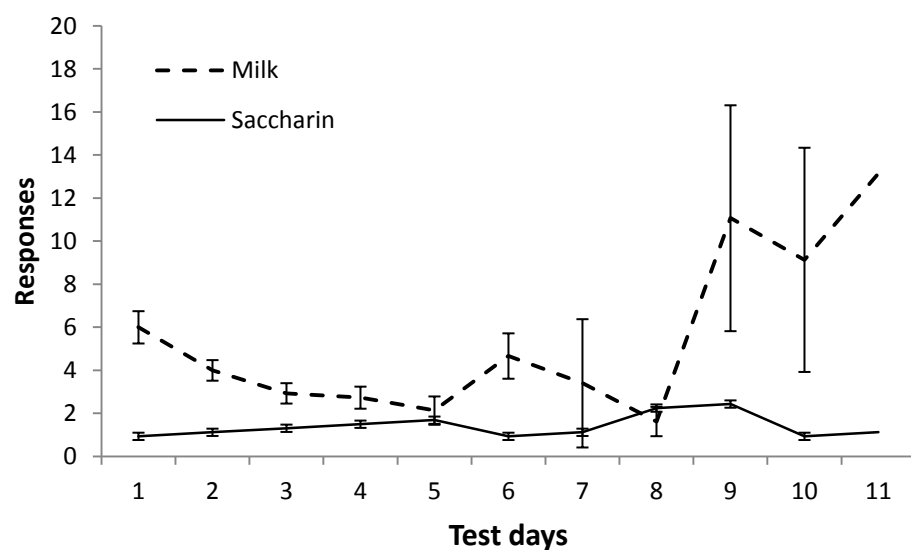
Responding continued to increase with repeated testing and about 80% of the rats had successfully acquired the nose poke operant with an additional 11 days of testing (Figure 5). Acquisition was achieved when animals made more than 80 correct responses within a session.



**Figure 5.** Percentage of rats that acquired nose poke behaviour when sweetened condensed milk served as the reinforcer.

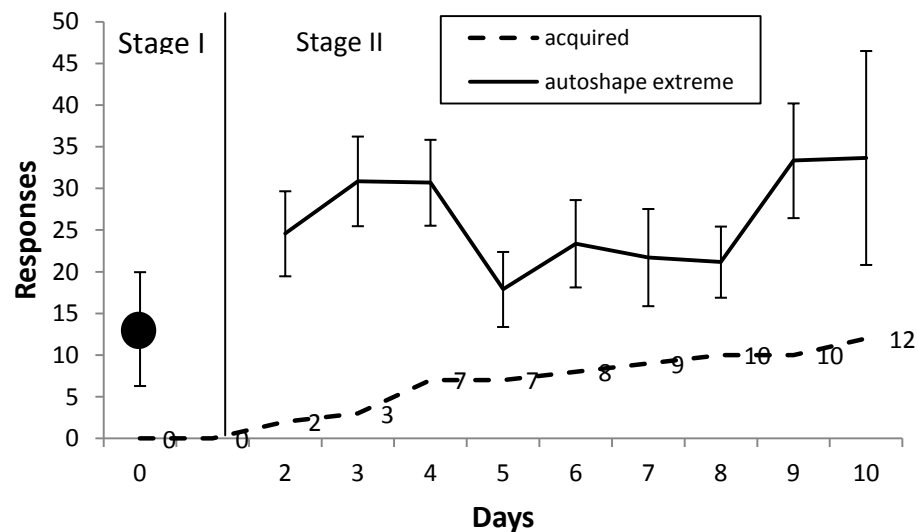
## Group 2

A second group of 16 rats was trained with sweetened condensed milk as the reinforcer. Although responding during the first 10 days of autoshaping was significantly higher than for the saccharin group (Group1), a large number of responses was still not produced within this time period (Figure 6,  $t = 3.499$ ,  $df=10$ ,  $p<0.01$ ).



**Figure 6.** Mean number of responses during the first 10 days of autoshaping for saccharin (Group 1) and sweetened condensed milk (Group 2). Responding for group 2 is significantly higher than for group 1 ( $p<0.01$ ).

In an attempt to speed up the autoshaping procedure, the procedure was altered so that all 5 lights were illuminated until a nose poke response was made into any of the 5 holes (Autoshape Stage II). Under these conditions, the number of responses increased and 75% (12/16) of rats acquired the nose poke behaviour (Figure 7).



**Figure 7.** Number of responses reinforced by sweetened condensed milk and cumulative number of rats that acquired nose poke behaviour during the autoshaping procedure in Group 2 (n=16). Day 1 marks the introduction of a new training stage (Autoshape Stage II). The numbers represent percentage of rats that acquired nose poke behaviour.

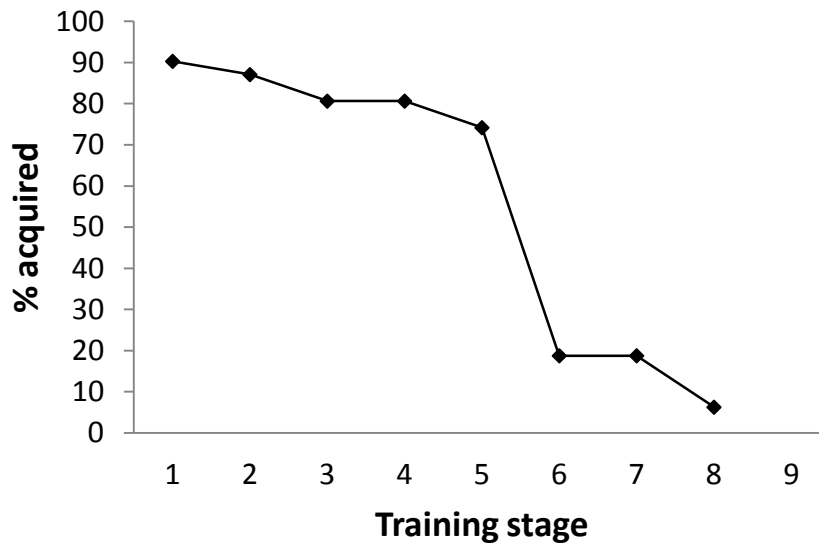
An additional procedure consisting of sweetened condensed milk as a reinforcer and three constitutive training stages as described in Table 2 (see II. General methods) was then imposed. A third group of rats (which subsequently became the first experimental group) was tested. Table 5 summarizes the main effects of these preliminary studies. The latency to acquire the nose-poke response dramatically decreased from 23.13 (Group 1) to 9.6 (Group 3) days (Student's T-test, Group 2 vs. Group 1:  $t = 3.413$ ,  $df = 29$ ; Group 3 vs. Group 1:  $t = 9.835$ ,  $df = 19$ , all  $p < 0.01$ ).

	<b>Days</b>	<b>Range</b>	<b>Comment</b>
<b>Group 1 (n=16)</b>	23.13	16-28	Ran first on saccharin, then on condensed milk (Autoshape I and III)
<b>Group 2 (n=16)</b>	18*	10-22	Only condensed milk (first Autoshape I and III when progress was still slow Autoshape Stage II was introduced)
<b>Group 3 (n=16)</b>	9.6*	8-14	Autoshape stage I, II and III

**Table 5.** Summary of progress of shaping nose poke behaviour over the first 3 groups of rats. Group 3 was the first experimental group. \* Group 2 and Group 3 differ significantly from Group 1, all  $p < 0.01$

### **Baseline criteria of performance**

Subsequent to acquiring nose poke behaviour, animals (Group 1 and Group 2) were trained according to the protocol described in Table 3 (see II. General methods). In short, across training sessions stimulus duration is progressively decreased while the ITI is increased. The target parameter was training level 12 (0.5 s stimulus duration and 5s ITI) as described in the original protocol of Bari et al. (2008). Despite extensive training (~ 40 sessions) acquisition of responding required extensive testing and only one rat progressed to training level 7. A notable characteristic of performance was a dramatic decrease in performance after level 5 of the training protocol, as evident in Figure 8.



**Figure 8.** Percentage of rats that reached criterion for the various training stages including Group 1 and Group 2 (n=32).

As a result, the target training parameter was set to level 5 for the remainder of the study. Table 6 shows the mean baseline performance across 5 consecutive days at level 5 compared to the baseline performance of adult male Lister hooded rats in a previous study across 5 days at level 12 (Bari et al. 2008). Although there is a clear match in accuracy, all other measures were clearly higher in the current study.

	Baseline	Sprague-Dawley Range	Lister hooded Baseline
<b>Accuracy (%)</b>	83.3 ± 1.5	68 – 96.2	80.7 ± 2.8
<b>Premature responses</b>	14.3 ± 1.7	2.8 – 30.2	6.6 ± 1.1
<b>Omission</b>	34.1 ± 3.6	4.6 – 80.2	5.8 ± 1.6

**Table 6.** Baseline performance on the 5-CSRTT of Sprague-Dawley (SD) (training level 5, n=24, mean ± SEM) and adult Lister hooded rats (n=9, mean ± SEM) (from Bari et al. 2008).



## *Discussion*

The purpose of these experiments was to establish reliable training and test parameter for the 5-CSRTT in SD rats. A range of parameters was applied in order to ensure efficient progress in training and reliable test criteria for the purpose of establishing a measurable and reliable baseline performance. In order to achieve this, days to acquisition and number of responses were measured as dependent variables.

Differences in equipment and rat strain made it necessary to adapt a commonly used version of the 5-CSRTT to our laboratory settings. When saccharin was used as a reinforcer, acquisition of the operant was delayed. Responding significantly increased and a larger percentage of rats acquired the operant when sweetened condensed milk was substituted. The introduction of an additional training stage (Autoshape II) further decreased the latency to acquisition of the nose poke response without changing the percentage of the group that acquired the operant. Once this effective autoshaping procedure was established, training for the 5-CSRTT began.

Because performance in the 5-CSRTT requires the ability to perceive a visual stimulus, performance by albino strains of rat might be compromised due to the relative lack of visual acuity (Heiduschka & Schraermeyer, 2008). One study demonstrated that albino, and in particular SD rats, performed less well than their pigmented congeners when comparing the learning abilities of several rat strains in memory tasks with a strong spatial component (Harker & Whishaw, 2002). Moreover, another study showed SD rats were unable to reach the performance criteria used by other laboratories (80% accuracy, 15% omissions) despite extensive training (Paine et al 2007). In general, pigmented rat strains performed more accurately compared to SD rats (accuracy approximately 80% and 60%, respectively) while the number of omissions and

premature responses were similar (Blondel et al., 2000; Mirza & Bright, 2001; Mirza & Stolerman, 1998). Modifications that improved performance included increased stimulus duration (1 sec instead of 0.5 s) in the final phase of training and testing (Hahn et al. 2002; Semenova et al. 2007), shorter session length of 30 min (Paine et al. 2007; Blondel et al. 2000), as well as altered criterion performance ( $> 60\%$  accuracy and  $< 20\%$  omissions) (Semenova et al. 2007; Blondel et al. 2000; Mirza & Bright 2001; Mirza & Stolerman 1998). Indeed, one recent study showed no significant differences in final performance between an albino and a pigmented rat strain using the 5-CSRTT when training and testing parameters were adjusted (e.g. a final stimulus duration of 1 s) (Auclair et al. 2009). In fact, SD rats acquired final task performance significantly faster than the pigmented rat strain (Auclair et al. 2009).

These findings might explain the dramatic decrease in performance beyond training level 5. Since stimulus duration was reduced from 2.5 s (Level 5) to 1.25 s (Level 6). Even when the stimulus presentation was increased to 2 s, the rapid decrease in performance was observed. Therefore, the study was limited to testing up to Stage 5.

One possible explanation for the increased percentage of omission was, that the equipment in the present study did not permit the new trial to be initiated by breaking a beam in the aperture, thus constant attendance to the stimulus throughout whole 45 min was required in order to successfully meet the criterion for acquisition. In the original version of the 5-CSRTT the initiation of the next trial is, in effect, “self-paced”, and a nose poke in the feeder hole starts the next trial. Thus, other behaviours (e.g. grooming) during this period, would not impact performance. The present version might, therefore, be expected to result in an increase the percentage of omitted trials as was observed in this and another study (Semenova et al. 2007). Parameters of an accuracy level of 65% and omission rate of 35% were used.

## **Chapter 2: Relationship between impulsivity and novelty seeking and the acquisition of MDMA self-administration**

(These findings have been published in Bird and Schenk (2012). Contribution of impulsivity and novelty-seeking to the acquisition and maintenance of MDMA self-administration. *Addiction Biology*, doi: 10.1111/j.1369-1600.2012.00477.x. [Epub ahead of print])

### *Overview*

Some studies have suggested that certain traits might be linked to the transition from occasional drug use to drug dependence. Among those, it has been suggested that individuals high in impulsivity and/or sensation seeking might be particularly susceptible (Kelly et al. 2006; Moeller et al. 2001; Martin et al. 2002). Like other drug users, ecstasy users exhibit greater impulsivity (Butler & Montgomery, 2004; Hanson, Luciana & Sullwold. 2008) even after prolonged abstinence (Morgan et al. 2002). It remains unclear, however, whether these psychobiological traits existed prior to, or followed, long-term drug use.

Animal studies are particularly well suited to address this question since the acquisition and maintenance of drug taking can be measured. Sensation-seeking has been modelled in laboratory animals as a response to a novel environment (Piazza et al., 1989) because of the similarity to the concept in humans, as defined by Zuckerman (1984). Impulsivity has been measured in laboratory animals through the use of the 5-choice serial reaction time task (5-CSRTT) (Bari, Dalley & Robbins 2008; Robbins, 2002). Unlike the response to novelty, however, initial measures of impulsivity did not predict the latency to acquisition of drug self-administration (Dalley et al. 2007a). Thus,

sensation-seeking and impulsivity might predict different stages of dependence (Belin et al., 2008; Dalley et al., 2007a).

Animals were first trained in the 5-CSRTT and screened for impulsivity. Catheter implantation followed one week after these baseline tests. Subsequently, animals were screened for novelty-seeking before self-administration tests began.

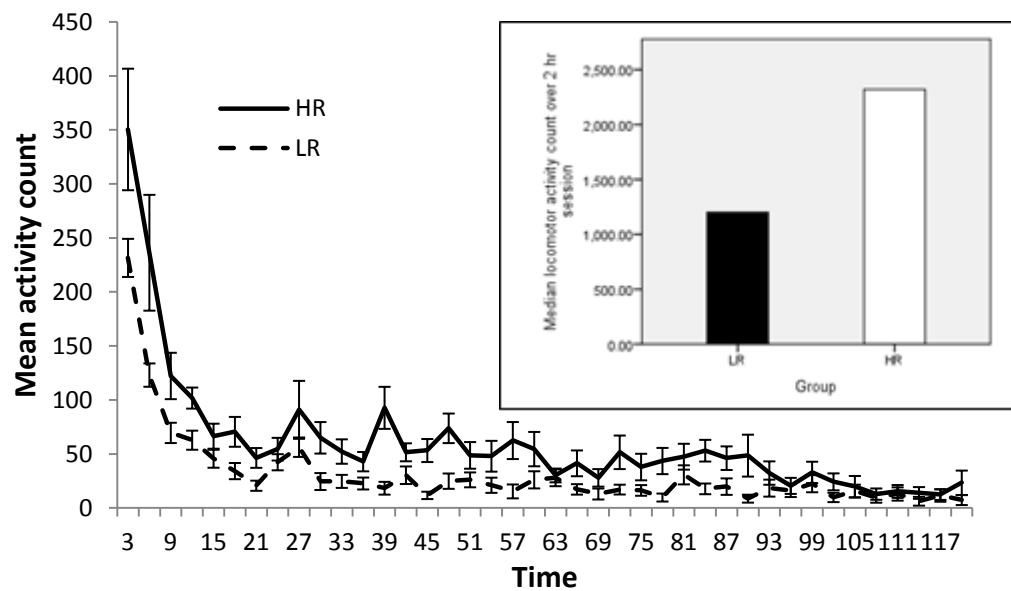
## Results

Table 7 shows the data obtained for the behavioural and novelty-seeking tasks prior to MDMA self-administration. Both, premature responses and omissions were normally distributed. Accuracy and novelty scores were not normally distributed and so the median is presented. HR showed significantly more locomotor activity across the 2 hr test session than LR (Figure 9,  $t(20)=-4.73$ ,  $p<0.01$ ). Novelty seeking and impulsivity were not significantly correlated ( $r = 0.185$ , NS).

Test	acquired	measurement	score (mean $\pm$ SEM)
5-CSRTT (n=104)	n=46	accuracy	84.8 <sup>1</sup>
		premature	18.6 $\pm$ 1.24
		omission	44.6 $\pm$ 2.7
novelty seeking (n=26)		novelty seeking	1570 <sup>1</sup>

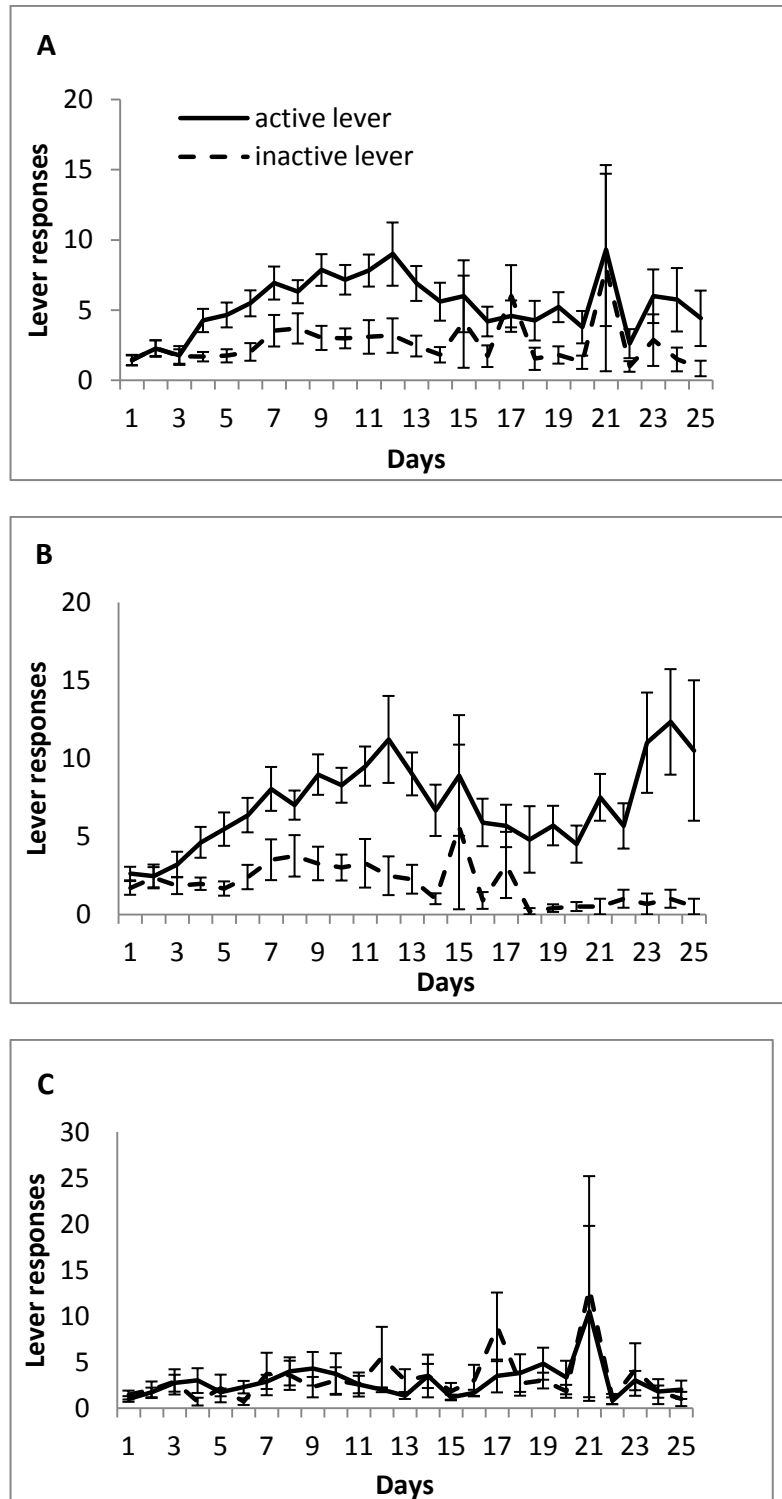
(1) Novelty seeking and accuracy were not normally distributed and are presented as the median score.

**Table 7.** Acquisition of the 5-CSRTT and novelty seeking.



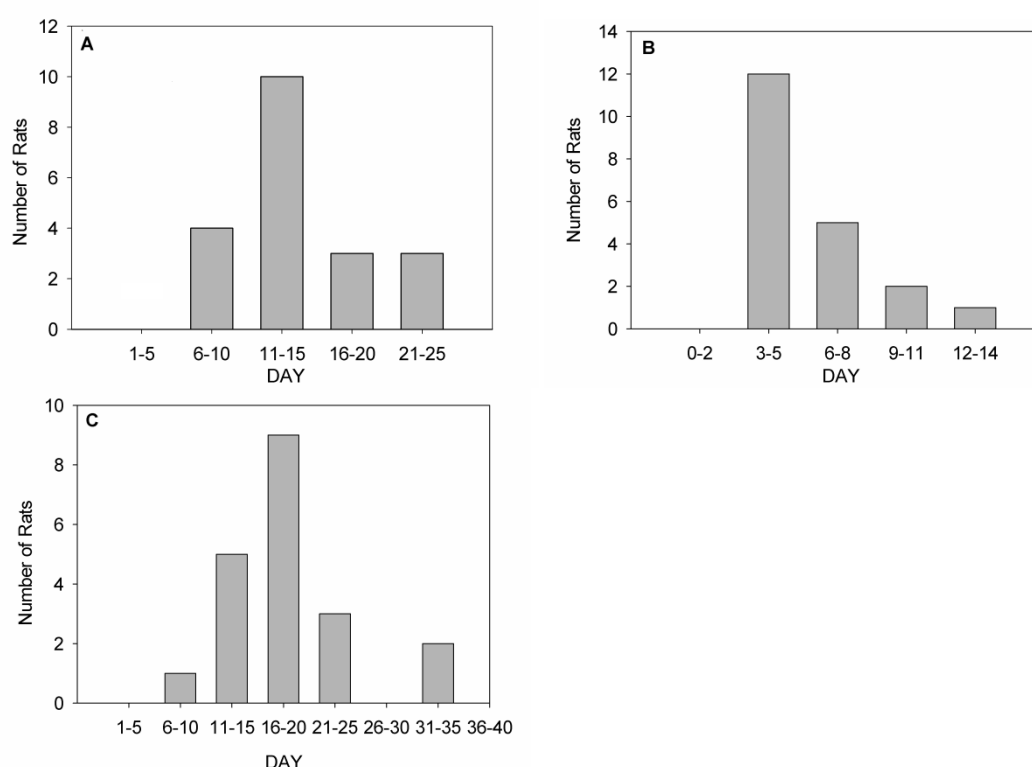
**Figure 9.** Locomotor activity count as a function of time bin (3 min bins). Data is presented for high (HR) and low responders (LR) based on a median split. HR and LR significantly differed in their median response to a novel environment ( $t(20)=-4.73$ ,  $p<0.01$ ).

The impulsivity scores for the 26 rats that met the criterion within 25 days (mean= 18.28) and for the 8 rats that did not meet the criterion (mean= 17.53) were not significantly different ( $t(32)= 0.181$ , NS). Responding for MDMA increased as a function of session for rats which acquired the behaviour (Figure 10B) and those rats showed discriminative responding between active and inactive levers as opposed to a group of rats which did not acquire (Figure 10C) ( $F_{1,25}= 62.96$ ,  $p<0.01$  and  $F_{1,6}<1$ , NS, respectively).



**Figure 10.** Active and inactive lever responding for 1.0 mg/kg MDMA infusions for the initial 25 days. (A) shows discriminative active lever responding for the total group (acquired and not acquired;  $n=33$ ) ( $p<0.01$ ), (B) shows discriminative active lever responding for rats that acquired MDMA self-administration ( $n=26$ ) ( $p<0.01$ ), (C) shows that a group of rats which did not acquire MDMA self-administration ( $n=7$ ) did not discriminate between active and inactive lever ( $p>0.05$ ).

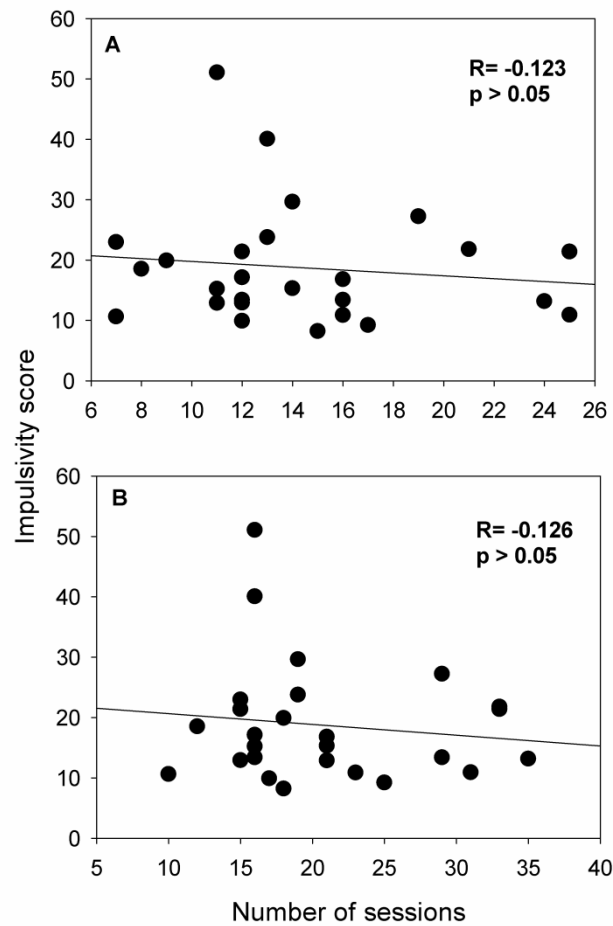
The initial 90 infusions of 1.0 mg/kg MDMA were self-administered in an average of 14.67 days ( $\pm 0.95$ ) and the subsequent 150 infusions of 0.5 mg/kg were self-administered in an average of 6.21 days ( $\pm 0.56$ ). Figure 11 shows the frequency distribution for the number of rats that met the initial criterion of 90 infusions of 1.0 mg/kg (Figure 11A), the subsequent criterion of 150 infusions of 0.5 mg/kg (Figure 11B) and the total 240 infusions (Figure 11C) as a function of days of testing.



**Figure 11.** Frequency distribution for the acquisition of MDMA self-administration as a function of days (n=26). (A) days to self-administer the initial 90 infusions of 1.0 mg/kg/infusion MDMA; (B) days to self-administer the subsequent 150 infusions of 0.5 mg/kg/infusion MDMA; (C) days to self-administer the total of 240 infusion of MDMA.

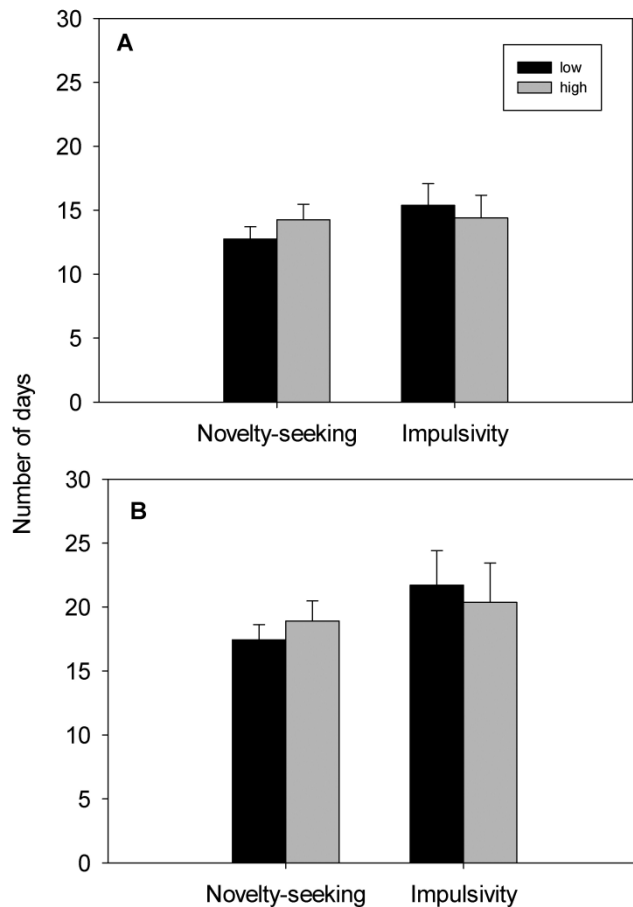
The correlations between impulsivity and latency to self-administer the initial 90 infusions of 1.0 mg/kg MDMA or with the latency to self-administer the entire 240 infusions of MDMA were not significant (see Figure 12). For completeness it should be

mentioned that the 150 infusions of 0.5 mg/kg MDMA also did not prove significant ( $r = -0.031$ , NS).



**Figure 12.** Latency to acquisition as a function of days required to self-administer the (A) initial 90 infusions of 1.0 mg/kg MDMA (90 mg/kg MDMA) ( $r = -0.123$ , NS) or (B) the entire 240 infusions (165 mg/kg MDMA) ( $r = -0.126$ , NS).

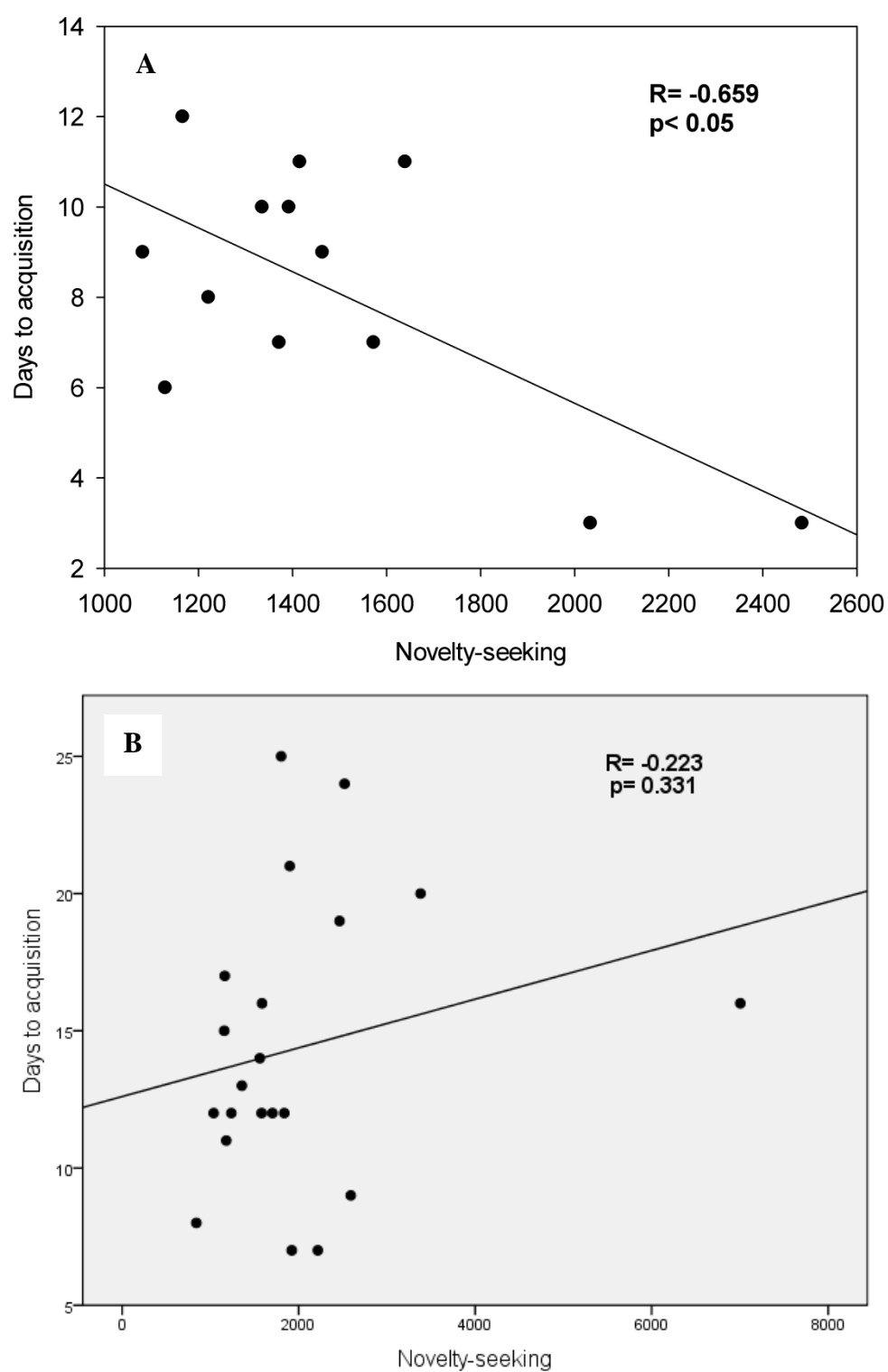




**Figure 13.** Latency to self-administer the initial 90 infusions of 1.0 mg/kg MDMA (A) and the latency to self-administer the total 240 infusions (165 mg/kg MDMA) (B) for high and low impulsive or novelty-seeking groups based on a median split. Symbols represent the mean latency ( $\pm$  SEM).

When a median split was applied in order to compare high and low impulsive or novelty seeking groups, there was no significant difference in latency to acquisition of MDMA self-administration for the initial 90 infusions (Figure 13A) or the total 240 infusions (Figure 13B).

To validate the measure of novelty-seeking a further group of rats ( $n=16$ ) was tested for acquisition of cocaine self-administration. Three rats were excluded because their self-administration data was affected. One rat lost catheter patency during self-administration and the other two exhibited high responses on the inactive (left) lever. A



**Figure 14.** Relationship between latency to acquisition of (A) cocaine and (B) MDMA self-administration and novelty-seeking.

preference for the active (right) lever could not be concluded and therefore, responding might have been, at least partially, due to motor activation. Although student t-tests did not show a difference between HR and LR, there was a robust correlation (Figure 14) between novelty-seeking and days to acquisition ( $r = -0.659$ ,  $p < 0.05$ ).

### *Discussion*

The idea that the response to novelty in rat subjects might predict the initial response to the positively reinforcing effects of drugs of abuse is based on the hypothesis that this response is a valid measure of the trait of sensation seeking in humans. High sensation seekers were more likely to experiment with various illicit drugs (Martin et al. 2002; 2004), were more responsive to some drugs of abuse as measured by various scales of the ARCI, POMS and VAS that measure positive subjective effects (Stoops et al., 2007; Kelly et al., 2006; but see Corr & Kumari, 2000) and also demonstrated greater incentive motivation to self-administer amphetamine in a laboratory setting (Stoops et al., 2007). In the laboratory, rats that were more responsive to novelty acquired cocaine (Belin et al. 2008) and amphetamine (Piazza et al., 1989) self-administration with a shorter latency.

The failure to observe a relationship between novelty-seeking and MDMA self-administration might be due to the unique pharmacology of MDMA. Unlike many other drugs of abuse, acute exposure to MDMA preferentially enhances synaptic 5HT (Baumann et al., 2005; Kankaanpää et al. 1998; De Souza, Battaglia, Insel 1990). We have suggested that this is why MDMA does not initially support high rates of self-administration (Schenk, 2011). This might also explain why the novelty response, which has been attributed to DAergic mechanisms (Bardo, Donohew, Harrington et al. 1996), was not related to the latency to acquisition of self-administration.

Although the predominant effect of initial exposure to MDMA is to increase synaptic 5HT, this response becomes compromised following repeated exposure. Thus, tissue levels of 5HT were decreased following repeated exposure (Schmidt, Wu, Lovenberg, 1986; Mokler, Robinson, Rosecrans, 1987; Schenk et al. 2007; Colussi-Mas et al., 2010) and the MDMA-produced increase in synaptic 5HT was decreased (Shankaran & Gudelsky, 1999; Reveron, Maier, Duvauchelle, 2010). We have suggested that the development of MDMA self-administration proceeds as a result of these effects. The variability in the latency to acquisition of MDMA self-administration, therefore, might be due to differences in the progression of the 5HT deficits.

We hypothesized that these differences might, in turn, be a function of pre-existing differences as reflected in trait impulsivity. There is a large body of evidence suggesting that subjects high in impulsivity, as measured by premature responding in tasks like the 5CSSRT, become more highly motivated to self-administer drugs and are more likely to relapse to drug-taking following a period of abstinence (Winstanley et al., 2010 for review). Some preclinical studies have suggested that high impulsivity predisposes to the escalation of cocaine intake that occurs with extended testing (Dalley et al. 2007a; Anker et al. 2009) and to the development of cocaine-seeking (Belin et al. 2008; Economidou et al. 2009).

In the present study, there was no relationship between impulsivity and the latency to acquisition of MDMA self-administration. The possibility that impulsivity might have predicted the propensity for self-administration to escalate with longer duration sessions was not directly assessed but can be addressed to a limited extent by comparing the impulsivity scores for the rats that acquired and did not acquire self-administration. For the former group there is an escalation of intake with repeated testing whereas for the latter group responding remains low and relatively invariable. Despite these differences in escalation of responding for the two groups, initial

impulsivity scores were comparable. A more adequate test of this hypothesis would, of course, require more extensive testing aimed at quantification of response patterns during the maintenance phase of self-administration following more extensive exposure to self-administered MDMA.

The present study used the range of impulsivity scores, whereas other studies have increased the range of impulsivity scores by using a longer ITI, and then grouping rats into high and low impulsive categories on the basis of a median split. Often those with only the lowest and highest scores are included for analysis. This approach reduces the variability substantially by measuring the behaviour of rats that produced only the extreme scores. Our interest, however, was to determine whether the variability in latency to acquisition of MDMA self-administration could be explained by initial impulsivity and we therefore correlated the two measures and used the entire range of scores for each variable. The most parsimonious interpretation of the data is that impulsivity did not predict either the latency to acquisition of MDMA self-administration or the escalation of intake that occurs with repeated testing.

### **Chapter 3: Drug seeking**

(These findings have been published in Bird and Schenk (2012). Contribution of impulsivity and novelty-seeking to the acquisition and maintenance of MDMA self-administration. *Addiction Biology*, doi: 10.1111/j.1369-1600.2012.00477.x. [Epub ahead of print])

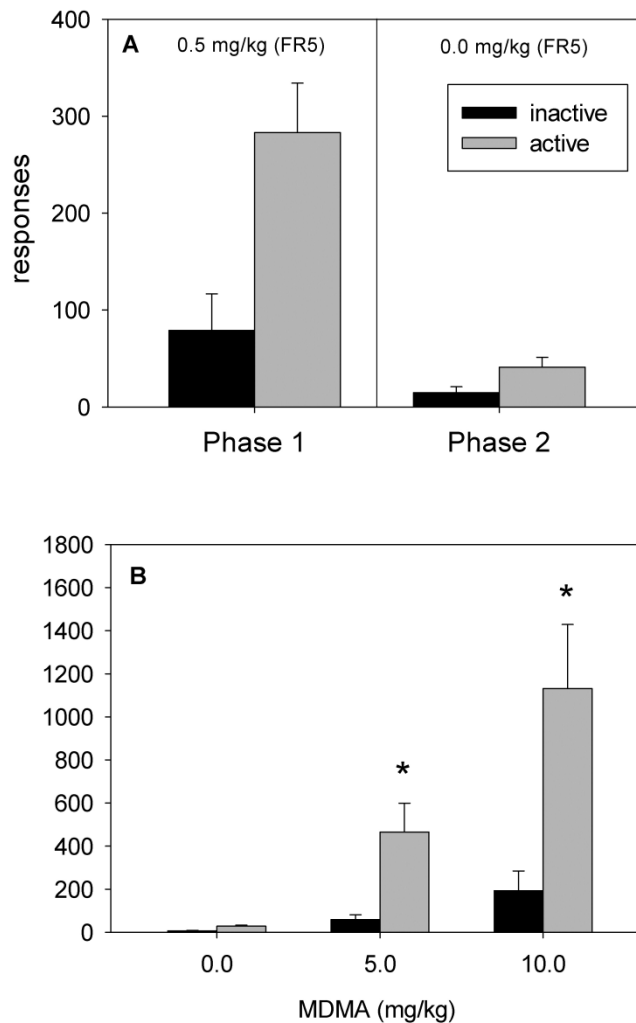
#### *Overview*

Following acquisition of MDMA self-administration (a total of 150 infusion) a group of rats (n=11) was tested for their drug-seeking response to MDMA priming injections. For drug-seeking tests the reinforcement schedule was increased to FR 5 and the session length was increased to 6 hours. Following at least 7 days, tests of drug-seeking began. Cannula patency failed for 4 of the rats before all of these data could be collected leaving a final sample size of 7.

Drug seeking was assessed during a recurring set of tests comprised of 3 phases as described in the General methods. MDMA priming injections (0.0, 5.0 and 10.0 mg/kg, IP) were administered and responding maintained by vehicle and the light stimulus was recorded, as demonstrated per previous studies (Schenk et al. 2008; Schenk et al. 2011a). All rats received all doses of MDMA administered in random order.

## *Results*

During the 2 days that comprised Phase 1 an average of 28.3 mg/kg/day was self-administered and there was a marked preference for the active lever (Fig. 15A).



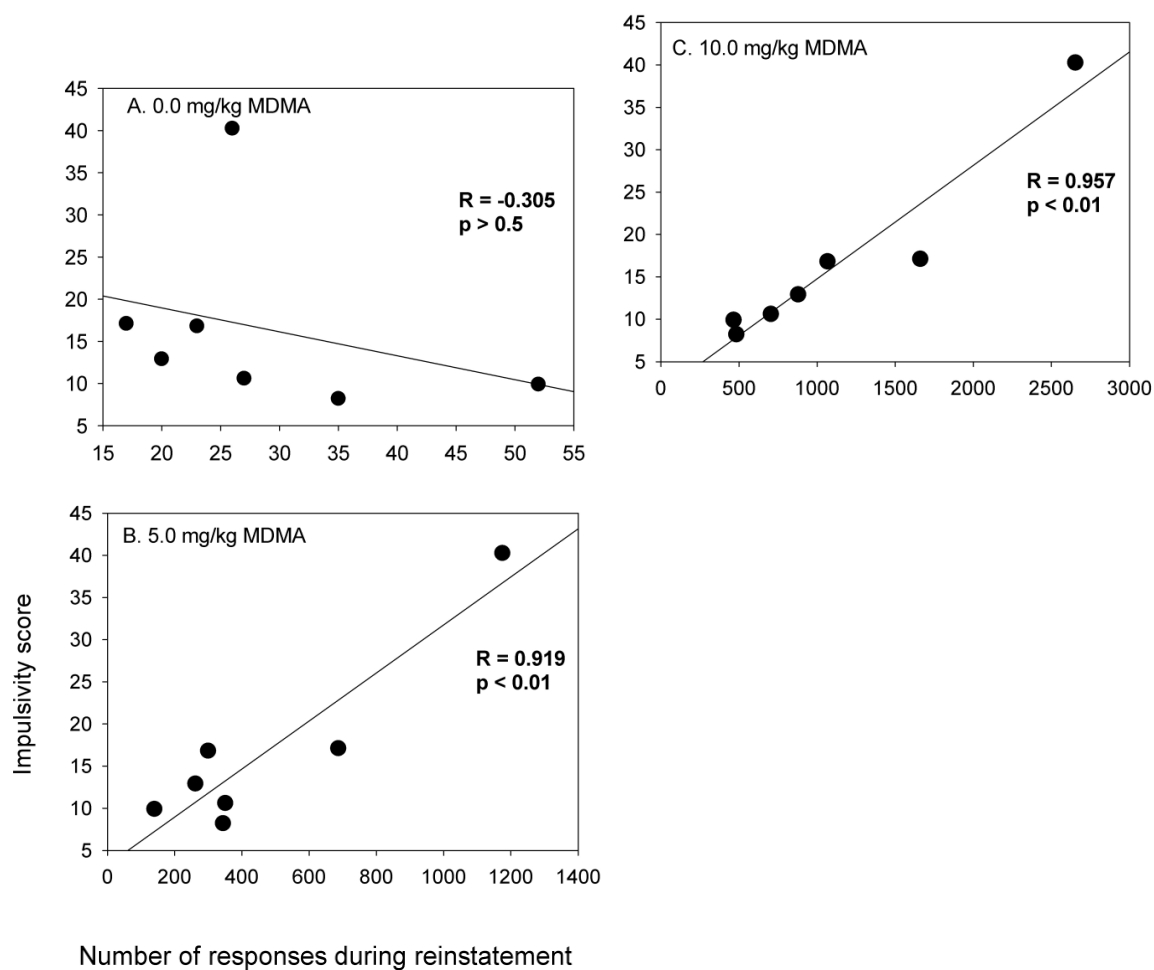
**Figure 15.** Presented are the mean number of responses ( $\pm$  SEM) during Phase 1 and 2 (A) and Phase 3 (B) of drug-seeking tests (\*  $p < 0.05$ ).

When MDMA was replaced with vehicle and the light that had been associated with self-administered MDMA infusions was omitted during Phase 2, responding decreased. The number of days required to meet the extinction criterion of  $< 30$  responses was  $3.57 (\pm 0.68)$ . Neither impulsivity nor novelty seeking were significantly correlated with the number of responses produced during the first extinction phase ( $r = -0.218$ ,  $p > 0.6$  and  $r = 0.086$ ,  $p > 0.8$ , respectively). MDMA, administered at the start of Phase 3, reinstated extinguished responding in a dose-dependent manner (Figure 15B). Mauchly's test indicated that the assumption of sphericity had been violated for dose

( $\chi^2(5) = 16.559$ ,  $p < 0.01$ ) and dose\*lever ( $\chi^2(5) = 7.512$ ,  $p < 0.05$ ), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ( $\epsilon = 0.509$  and  $\epsilon = 0.563$ ). A two-way repeated measures ANOVA (lever x dose) revealed significant main effects of dose ( $F_{1,6} = 13.227$ ,  $p < 0.05$ ) and lever ( $F_{1,6} = 17.964$ ,  $p < 0.01$ ), and a significant interaction ( $F_{1,6.8} = 16.670$ ,  $p < 0.05$ ). Post hoc comparisons confirmed that the doses of 5.0 mg/kg and 10.0 mg/kg MDMA increased responding relative to the 0.0 mg/kg dose ( $p < 0.05$ ).

Impulsivity ratings and novelty seeking scores were not correlated for this subset of rats ( $r = 0.616$ , NS). There was further no significant relationship between novelty seeking and drug-seeking following any dose of MDMA ( $p > 0.05$ ). Figure 16 shows, however, that impulsivity scores and the number of responses produced following 5.0 and 10.0 mg/kg MDMA, but not 0.0 mg/kg, were positively correlated. It is possible that the high positive correlations following 5.0 and 10.0 mg/kg MDMA were primarily due to the single apparent outlier at the extreme right of each graph. Excluding this data point from our analysis had little impact on the relationship between impulsivity and responses following 10.0 mg/kg MDMA ( $r = 0.905$ ,  $p < 0.05$ ). The correlation with responses following 5.0 mg/kg MDMA dose was, however, no longer significant when the data point was excluded ( $r = 0.551$ ,  $p = 0.25$ ). These findings are consistent with the general low level of responding produced following exposure to this low dose of MDMA (present results; Schenk et al. 2008).





**Figure 16.** Relationship between impulsivity and drug-seeking following 0.0 (A), 5.0 (B), and 10.0 (C) mg/kg MDMA.

### Discussion

In order to determine the relationship between impulsivity and drug-seeking, reinstatement of drug seeking was measured following extinction of MDMA self-administration after substantial exposure (average total amount of self-administered MDMA:  $417.28 \pm 25.49$  mg/kg; range of total exposure for the group: 357.0-550.0

mg/kg). Cue-produced drug-seeking (0.0 mg/kg MDMA) was not correlated with initial impulsivity score. The magnitude of the potentiation of the cue response produced by injections of either 5.0 or 10.0 mg/kg MDMA was, however, significantly correlated with the initial measure of impulsivity. These findings are consistent with the idea that drug-seeking in response to the presentation of a cue that had been associated with self-administered infusions and the potentiation of this drug-seeking response produced by drug primes are mediated by systems that are differentially related to impulsivity. Possibly, a longer drug free period would have revealed an impact of impulsivity on cue-produced drug seeking, as has been observed in another study (Economidou et al. 2009). Alternatively, the influence of impulsivity on drug seeking in response to the cue might be dependent on the self-administered drug since positive results have been obtained when cocaine (Economidou et al. 2009) but not heroin (McNamara et al. 2010) self-administration was measured.

Because of the pharmacology of MDMA related to its self-administration, a potential role of DA and/or 5HT in impulsivity could explain the relationship with drug seeking. Reinstatement of MDMA-seeking was potentiated by DA, but not 5HT, agonists and was attenuated by DAergic antagonists (Schenk, Gittings, Colussi-Mas, 2011). Further, the magnitude of the drug-seeking response was positively related to MDMA-produced increased DA (Colussi-Mas et al., 2010). Some studies also suggest that impulsivity is mediated by DAergic substrates (Aron 2007; Pattij & Vanderschuren, 2008). For example, premature responding on the 5-CSRTT was attenuated by DA antagonists and potentiated by DA agonists in some studies (for a detailed review see Dalley, Everitt & Robbins. 2011). There is evidence that pharmacological manipulations of 5HT can also impact both drug-seeking (Grottick, Fletcher, Higgins, 2000; Schenk et al. 2011a) and impulsivity (Harrison et al. 1997a; Winstanley et al. 2004; Fletcher et al. 2007), but the effects of these manipulations have been attributed

to a modulation of DAergic substrates (McMahon, Filip, Cunningham, 2001). Thus, the predicted relationship between impulsivity and drug-seeking might reflect pre-existing differences in the DAergic response to MDMA. An important test of this idea will be to measure initial and subsequent neurochemical responses to MDMA to determine whether these differences can explain both the impulsivity and self-administration data.

#### **Chapter 4: Effects of MDMA self-administration on impulsivity**

(These findings have been published in Bird and Schenk (2012). Contribution of impulsivity and novelty-seeking to the acquisition and maintenance of MDMA self-administration. *Addiction Biology*, doi: 10.1111/j.1369-1600.2012.00477.x. [Epub ahead of print])

##### *Overview*

There is a large body of literature describing various cognitive impairments following long-term drug abuse (Ornstein et al. 2000; Lundqvist, 2005; Fernandez-Serrano et al. 2010; King et al. 2010). Although MDMA initially elevates 5-HT levels it has been shown to decrease 5-HT levels in the brain after repeated experimenter administered or self-administered exposure (Schmidt et al. 1986; Battaglia et al. 1988; Schenk et al. 2007; Do & Schenk, 2011). Accordingly, evidence from human studies support the existence of psychobiological deficits after regular and frequent ecstasy use. 5-HT is involved in regulating an array of behaviours like sleep, appetite, mood, motivation, attentional processes and impulsivity. For example, ecstasy users (as measured by self-report inventories) had higher impulsivity levels (Morgan 1998, Butler & Montgomery, 2004) which are consistent over time, even during a period of

abstinence (Morgan et al. 2002), although it is unclear whether this psychobiological abnormality existed prior to, or followed long-term drug abuse. In animals, the 5HT deficits following MDMA self-administration have been associated with cognitive memory impairments (Schenk et al. 2011) and depletion of brain 5HT has been linked to elevated impulsivity levels (Harrison et al. 1997).

The aim was to determine if impulsivity was altered following chronic MDMA self-administration of a dose that has previously been shown to produce deficits in brain 5HT.

## *Results*

Figure 17 summarizes the effects on 5-CSRTT performance prior to and after MDMA self-administration. The data are presented for each of the 5 days prior to and 20 days following self-administration. Analyses were conducted on data collapsed into 5 day bins. Prior to self-administration tests there were no significant differences in the three dependent variables (All F-values < 1, NS).

### Omissions

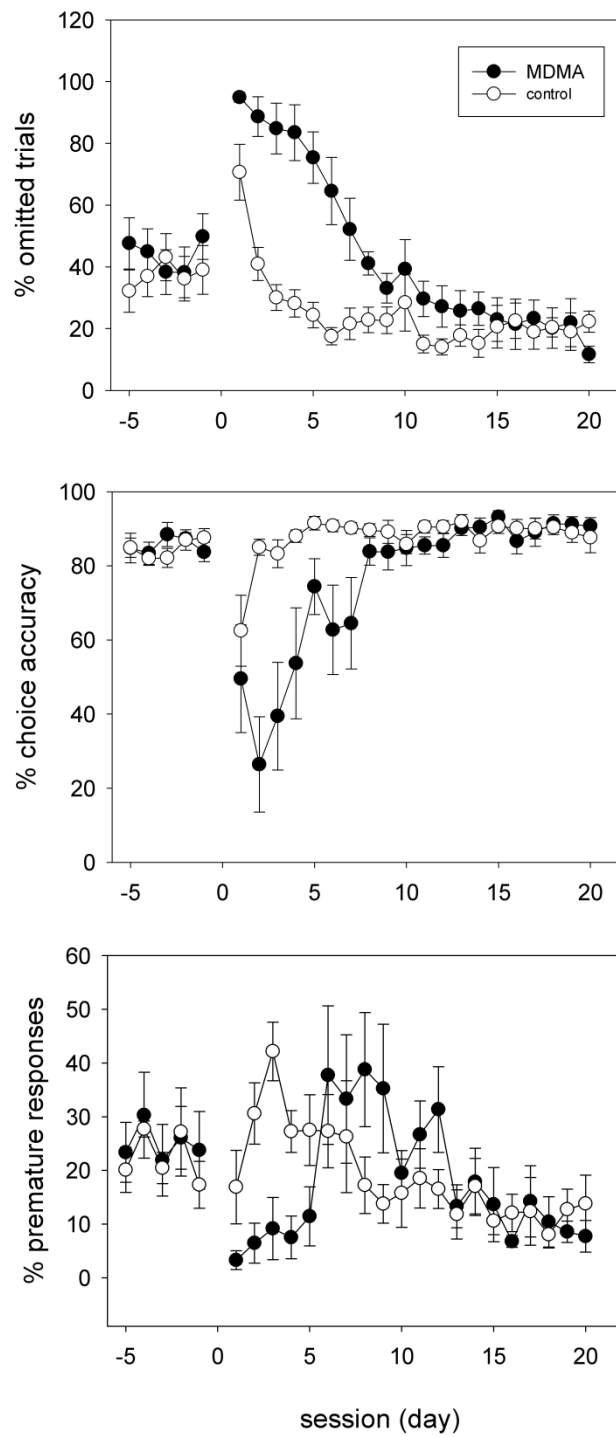
There was a sharp rise in omissions during the first 7 sessions for the MDMA group with a return to control levels two weeks after the last self-administration session. ANOVA revealed a significant *bin x group* interaction ( $F_{3,39} = 25.848, p < 0.01$ ). Omissions significantly decreased during bins 1 (days 1-5) ( $t(13) = -6.681, p < 0.01$ ) and 2 (days 6-10) ( $t(13) = -3.241, p < 0.01$ ) but not during subsequent bins.

### Choice accuracy

The high rate of omissions for the MDMA group precluded computation of a reliable measure of accuracy and MDMA self-administration produced an initial decrease in correct responses. Thus, ANOVA revealed a significant *bin x group* interaction ( $F_{3,39} = 10.066, p < 0.01$ ) with a significant reduction in correct responses in bin 1 ( $t(8) = 3.531, p < 0.01$ ). Accuracy recovered 10 days after the last self-administration session (Figure 17), as the number of omissions decreased.

#### Premature responses

MDMA self-administration decreased premature responding, although this measure was also markedly influenced by the overall decrease in responding during the initial test sessions following self-administration. This decrease was followed by a sharp but transient increase in premature responding. ANOVA revealed a significant *bin x group* interaction ( $F_{3,39} = 7.218, p < 0.01$ ) and t-tests confirmed a significant decrease during bin 1 ( $t(8) = 4.991, p < 0.01$ ) (Figure 17) and an increase during bin 2 ( $t(8) = -2.871, p < 0.05$ ).



**Figure 17.** Performance levels in the 5-CSRTT prior to (days -5 – 0) and following MDMA or saline self-administration (days 1 – 20). Symbols represent the mean ( $\pm$  SEM).

## *Discussion*

The effects of MDMA self-administration on 5-CSRTT performance were tested. Interestingly there were significant deficits in all three measures (accuracy, premature responses and omission) during the first 5 days of testing. Two weeks following self-administration, performance returned to controls levels. Thus, the present findings are in agreement with previous work (Dalley et al. 2007b) showing an initial, but transient, increase in premature responses, and a decrease in accuracy and omissions during acute withdrawal. It is noteworthy that there were a high level of omissions for the MDMA, but not the control group. The deficits in accuracy and the low impulsivity levels might, therefore, be due to a lack of motivation (as indexed by a high level of omissions) or deficits in memory (which has also been shown to be a consequence of MDMA self-administration; Schenk et al. 2011b). Regardless, the apparent deficits are a direct consequence of the high number of omitted trials, and effects of MDMA self-administration on impulsivity during these early test days could not be unambiguously determined.

## **Excursus: Acquisition of MDMA self-administration**

### *Overview*

An unexpected observation from the initial experiments for acquisition of MDMA self-administration was an extremely high acquisition rate for rats which were previously trained in the 5-CSRTT compared to a large standard cohort of rats. Of the

34 rats which started self-administration tests 26 rats (81%) reached the criterion amount of infusions within the 25 day cut off time compared to 30 rats (49%) out of a large cohort of rats (n=63) from our laboratory. Possible reasons for this difference included an effect of handling, as animals were trained on the 5-CSRTT for approximately 6 weeks prior to self-administration (Condition 1). The training itself could have acted as a filter and only more capable rats that quickly learned the 5-CSRTT, would progress to self-administration tests (Condition 2). Furthermore, the exposure to sweetened condensed milk during the 6 weeks of training offers two possible explanations for the effect: (1) the exposure to a sweet reinforcer might have sensitized rats for the reinforcing properties of MDMA, or (2) the exposure to a sweet reinforce acts like a filter and rats with a preference for sweet liking are more likely to acquire the 5-CSRTT (Condition 3). Indeed, some studies suggested that a preference of sweet-liking predicts subsequent drug self-administration (Carroll et al. 2002; Dess et al. 1998). To further investigate this effect two additional groups of rats were tested for their latency to acquisition of MDMA self-administration. Thus additional experiments measuring the effect of handling, the exposure a sweet reward, and the ability to acquire the 5-CSRTT were conducted to elucidate this observation (Table 8).



<b>Subjects/group</b>	<b>n</b>	<b>label</b>	<b>pretreatment</b>	<b>5-CSRTT</b>
<b>Experiment 1</b> (“Relationship between impulsivity and novelty seeking and the acquisition of MDMA self-administration”)	32	<i>Acquired 5-CSRTT</i>	<i>Food deprivation during 5-CSRTT training</i>	<i>Acquired 5-CSRTT</i>
<b>I75-I90</b>	12	<i>Not acquired 5-CSRTT</i>	<i>Food deprivation during 5-CSRTT training</i>	<i>Did not acquire the 5-CSRTT</i>
<b>Alpha – X-ray</b>	24	<i>Milk/water exposure</i>	<i>Food deprivation during pretreatment</i>	<i>Only exposed to the 5-CSRTT operant chambers while receiving either sweetened condensed milk or tap water</i>

**Table 8.** Overview of experimental groups. Rats from the initial study were compared to two additional groups of rats.

## *Results*

### Experimental groups

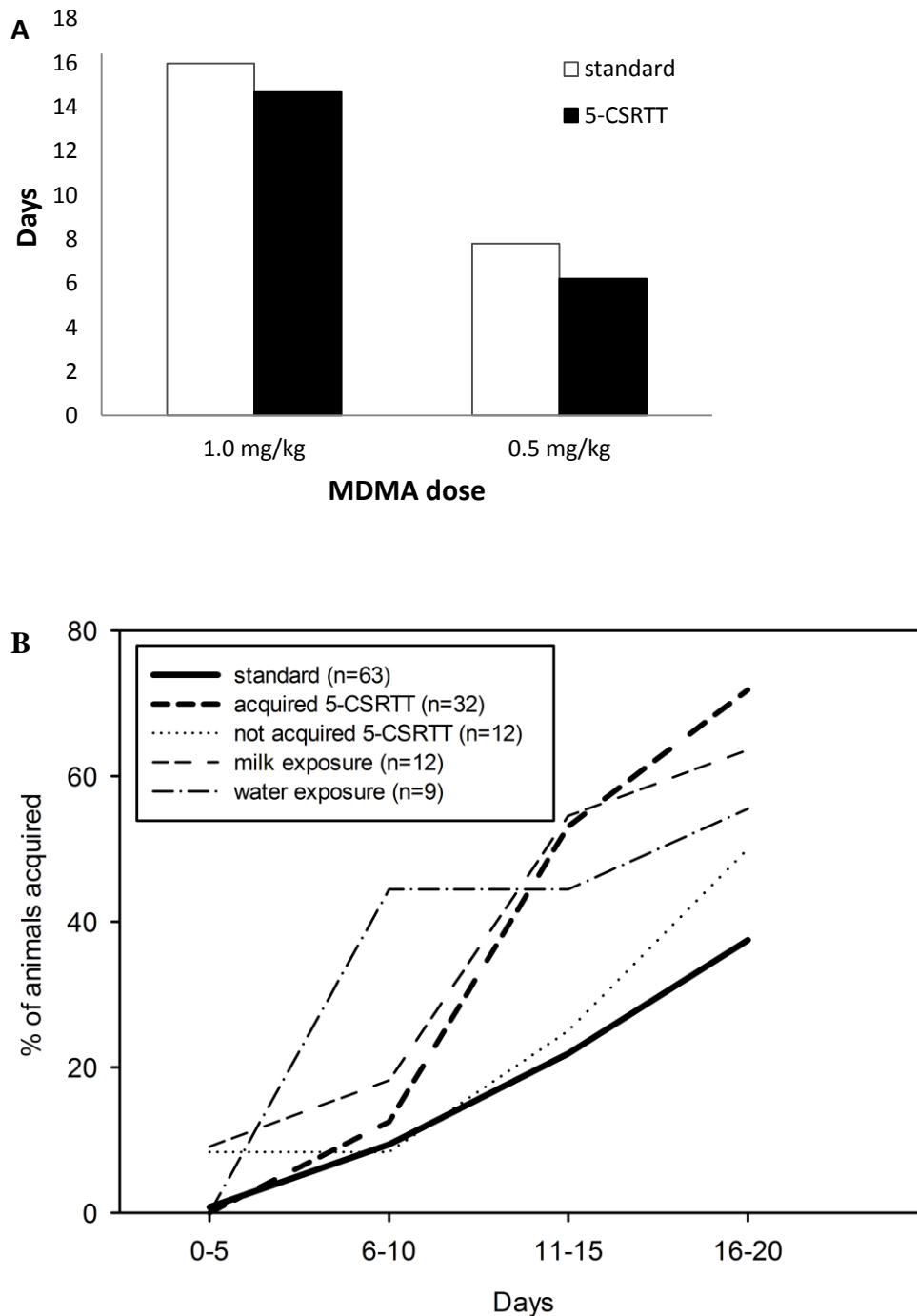
A summary of the two experimental groups can be found in Table 9. Group 1 consisted of a total of 15 rats that did not acquire the initial training stage in the 5-CSRTT. Those rats, although never exceeding the initial autoshaping phase, received the same amount of handling and daily exposure to the operant chambers before they progressed to MDMA self-administration.

Group	Condition	Duration	N-number
1	Not acquired 5-CSRTT	35	15
2	Milk exposure	35	12
	Water exposure	35	12

**Table 9.** Summary of the experimental groups.

A second group (Group 2, n=24) received the same treatment as the 5-CSRTT trained rats (daily handling, food deprivation, exposure to nine-hole boxes) with the only difference that 12 of those rats received 100 free reinforcers (sweetend condensed milk). The other 12 received tap water. The duration of this pretreatment procedure corresponded to the average time needed to successfully acquire the 5-CSRTT (35 days).

Despite the increased number of animals acquiring MDMA self-administration, Figure 18A shows that handling did not alter the latency to acquisition of MDMA self-administration. Rats which acquired the 5-CSRTT in the present study self-administered the initial 90 infusions of 1.0 mg/kg/infusion in an average of 14.67 days ( $\pm 0.95$ ) which did not differ from rats from the large cohort group which self-administered the 90 infusions in 15.97 days ( $\pm 0.67$ ) (Student's T-test,  $t = 1.294$ ,  $df = 87$ ;  $p > 0.05$ ). Days to acquire the 5-CSRTT did not correlate with the number of days to acquire MDMA self-administration ( $r = 0.05$ ; NS).



**Figure 18.** (A) Days to self-administer an initial 90 infusion of 1.0 mg/kg MDMA and the subsequent 150 infusions of 0.5 mg/kg MDMA for a standard cohort of rats (n=30) and rats previously trained in the 5-CSRTT (n=26). (B) Percentage of animals that self-administered the total of 240 infusions MDMA across all groups (acquired 5-CSRTT n=32; not acquired 5-CSRTT n=12; milk exposure n=12; water exposure n=9).

After the initial 90 infusions the dose of 1.0 mg/kg /infusion MDMA was reduced to 0.5 mg/kg/infusion and responding increased in a compensatory fashion until 150 infusion were self-administered in an average of 6.21 days ( $\pm$  0.56) and 7.8 days ( $\pm$  0.49) for both groups, respectively (Figure 18B. Student's t-test ,  $t= 1.204$ ,  $df=87$ ;  $p>0.05$ ).

$\chi^2$ -test revealed a significant difference in the proportion of rats acquiring MDMA self-administration between the rats that acquired the 5-CSRTT and the standard cohort (Table 10.  $\chi^2= 10.641$ ;  $p<0.01$ ). The group that did not acquire the 5-CSRTT did not differ from the standard cohort ( $\chi^2= 0.365$ ; NS). Furthermore, neither the group exposed to sweetened condensed milk nor the group exposed to water differed from the standard cohort ( $\chi^2= 1.336$  and  $2.746$ , respectively; both NS).

	5-CSRTT	no 5-CSRTT	Milk exposure	Water exposure
$\chi^2$	10.641	0.365	1.336	2.746
<b>Significance</b>	$p<0.01$	$p>0.05$	$p>0.05$	$p>0.05$

**Table 10.** Comparison of the percentage of rats acquiring MDMA self-administration across the different experimental groups compared to a large standard cohort of rats. Only rats that acquired the 5-CSRTT differed from significantly from the standard cohort.

## Discussion

A larger percentage of rats that successfully learned the 5-CSRTT acquired MDMA self-administration. Three groups of rats received different pre-treatment before MDMA self-administration in order to determine whether various aspects of training

might have increased the percentage of rats. Unfortunately, subject attrition was high due to loss of catheter patency.

Several possibilities that might explain the difference in acquisition rate were tested. For one, it is possible that only rats that learned the task in the destined time period also learned the operant for self-administration. It has been suggested that a difference in instrumental learning might underpin the propensity to acquisition as it has been shown that high impulsive rats (identified in a delay discounting paradigm) that acquired cocaine self-administration more rapidly (Perry et al. 2005) also acquired the delay-discounting task more rapidly. The lack of a correlation between days to acquire the 5-CSRTT and days to acquire MDMA self-administration in the present study makes this explanation rather unlikely. It might further be possible that the long training procedure, with prolonged food deprivation and extensive handling of the rats, had an effect on subsequent self-administration behaviour. Although handling rats is normally used to decrease stress there have been some studies which raise some doubt. Indeed, handling rats for 20 consecutive days significantly increased mean heart rate, blood pressure, and serum corticosterone (CORT) concentrations (Armario et al., 1986a, 1986b; Balcombe et al., 2004) all physiological markers of stress. Some studies suggested that this increase in CORT concentrations after the initial handling may affect performance in subsequent behavioural tests (Brown & Martin, 1974). Interestingly, there was minimal habituation to these physiological markers of stress (Balcombe et al., 2004). Therefore, daily handling may actually increase the stress response. Furthermore, it has been suggested that physical (such as, food deprivation) and psychological stressors facilitate the acquisition and maintenance of drug self-administration (Schenk et al. 1987; Piazza et al. 1990; 1991; Maccari et al. 1991; Deminiere et al. 1992; Ramsey & Van Ree 1993; Goeders & Guerin, 1994; Erb et al. 1996; Miczek & Mutscheler 1996) possibly because of enhanced DAergic effects (Piazza et al. 1990, 1991). It has been shown that, like

drugs of abuse, exposure to acute and repeated stress can increase DA release in the NAcc (Kalivas & Stewart, 1991). Furthermore, administration of glucocorticoid hormones can also augment synaptic DA in the NAcc (Piazza et al. 1996) while blocking glucocorticoid secretion had the opposite effect (Piazza et al. 1996). Additionally, if DA release is manipulated by other means, such as repeated administration of AMPH (Robinson & Berridge 1993; Piazza et al. 1990; Kalivas & Stewart 1991) or specific lesions of mesolimbic structures (Deminier et al. 1988; Schenk et al. 1991) a comparable effect on self-administration has been observed. This accumulation of evidence suggests that stress might sensitize a DAergic response to psychostimulant drugs and therefore might explain the high acquisition rate in the present study.

To determine the effect of handling and a possible learning effect on the acquisition of MDMA self-administration a group of rats that did not acquire the 5-CSRTT were tested for their acquisition of MDMA self-administration. These rats were handled to the same extent as rats that acquired the task. Interestingly, this group did not differ from the standard cohort. It has to be noted that the relatively low number of rats in this experimental group might limit the interpretation of the present results and further studies are necessary. It would be of great interest, for example, to test rats in a simple instrumental learning task before they are allowed to self-administer MDMA to extend the present results.

Rats that acquired the 5-CSRTT and those that did not also differed in their exposure to sweetened condensed milk. As rats that did not pick up the 5-CSRTT only received a very small number of rewards (~ 5) a further group of rats was tested to determine effects of exposure to sweetened condensed milk. It has been suggested that sweet liking constitutes a risk for drug abuse (Carroll et al., 2008; Dess et al., 1998). For

example, rats that were selected or selectively bred for high levels of sweet intake (HiS) compared with those for low sweet intake (LoS) self-administered more cocaine and a larger percentage acquired self-administration and they did so more rapidly (Carroll et al., 2002, 2007). Furthermore, HiS rats were more resistant to extinction and produced more responses during cocaine-primed reinstatement (Perry et al. 2006). In the present study, there was no difference between rats that were either exposed to sweetened condensed milk or water and the standard cohort. It has to be noted, that in the present study rats were not able to choose between a sweet or a non sweet reward and this might constitute a limitation in comparing these results to animal models of high versus low sweet intake. HiS will show a marked preference for a sweet reward compared to LoS (Carroll et al. 2002; Dess et al. 1998). A preference for sweetened condensed milk and subsequent self-administration was not determined in the present work. Finally, once more, low final numbers in the experimental groups might limit interpretation.

Although several reasons for the high acquisition rate were investigated none of the results were conclusive. In particular, small sample sizes prevented unambiguous interpretation of results. Nevertheless, the high acquisition rate was observed across all groups of rats that acquired the 5-CSRTT. Studies comparing acquisition profiles of rats that differ in learning abilities and their preference for sweet intake and food deprivation might offer more insight.

#### **IV. General discussion**

The aim of this thesis was to examine the relationship between trait impulsivity and novelty seeking on both the acquisition and maintenance of MDMA self-administration.

A wealth of literature has focused on the role of psychobiological traits and their contribution to the development of addiction. In particular, impulsivity (depicting a core feature of many psychiatric disorders comorbid to drug addiction) and sensation seeking have received special interest. Impulsivity and novelty-seeking have been proposed to be mediated by neural substrates that reflect different aspects of the addiction process (Belin et al. 2008; Dalley et al. 2007a). This thesis is the first study to investigate the role of these traits in MDMA self-administration. The main findings can be summarized as followed:

1. Impulsivity did not predict the latency to acquisition of MDMA self-administration but was positively correlated with the magnitude of the drug-seeking response induced by MDMA priming injections.
2. Novelty seeking it failed to predict MDMA self-administration.
3. There was a transient increase in impulsive responding following MDMA self-administration.
4. MDMA self-administration resulted in a high level of omissions during withdrawal.
5. Rats that acquired the 5-CSRTT were more likely to also acquire MDMA self-administration but this effect could not be explained by an effect of handling, food restriction, or exposure to sweetened condensed milk.

Initial daily number of responses maintained by MDMA is usually low but some animals eventually self-administer 20-30 mg/kg/day (Colussi-Mas et al. 2010; Do & Schenk, 2012; Schenk et al. 2003, 2007, 2008). The initial low rate of responding has been attributed to the predominant 5HTergic effects of MDMA. Because 5HT is inhibitory to self-administration (Clemens et al. 2006; Howell & Byrd, 1995; Peltier & Schenk, 1993; Smith et al. 1986; Wee & Woolverton, 2006), it has been suggested that



this neurochemical effect limits MDMA self-administration. With repeated exposure, however, MDMA produced 5HT deficits (Schenk et al. 2007, 2011a; Do & Schenk 2011) and it has been suggested that this might underlie the development of reliable self-administration (Schenk et al. 2011a, 2011b; Colussi-Mas et al. 2010). The precise consequence of the 5HT deficit has yet to be determined but a modulatory role on DA neurotransmission has been suggested, possibly mediated by structural and functional changes of various 5HT receptors and other transmitter proteins (Aguirre et al. 1997; Bonkale & Austin, 2008).

It is well known that DA is crucial for initiating and maintaining self-administration. Virtually all drugs of abuse increase DA in the NAcc (Di Chiara & Imperato 1988), and DA agonists are self-administered (Deneau et al. 1969; Schuster & Thomas 1969). Conversely, administration of DA antagonists decreased drug self-administration (Woolverton 1986; Rassnick et al. 1992; Richardson et al. 1994). Consistent with these observations, an important role of DA in the maintenance of MDMA self-administration has been demonstrated and DA antagonists also decreased responding maintained by MDMA (Brennan et al. 2009; Daniela et al. 2004). It has further been suggested that repeated exposure to MDMA sensitized DAergic substrates (Bradbury et al. 2012; Colussi-Mas et al. 2010) and rats pre-treated with MDMA acquired cocaine self-administration with shorter latencies (Fletcher et al. 2001). Conversely, rats which had previously self-administered cocaine acquired MDMA self-administration with a shorter latency (Schenk et al. 2003, 2007). Thus, the latency to acquisition of MDMA self-administration might depend on either the sensitivity to the deficits in 5HT or, alternatively, to the individual sensitivity to the DAergic effects of MDMA.

A relationship between vulnerability to drugs of abuse and high levels of novelty-seeking has been suggested to be mediated by mesolimbic DAergic activity (Piazza & Le Moal, 1996). High levels of novelty-seeking were correlated with basal DA (Hooks

et al. 1992; Piazza et al. 1991) and these rats subsequently acquired self-administration with shorter latency. Furthermore, those rats showed a higher and more persistent DA response in the NAcc following cocaine and amphetamine administration (Hooks et al. 1992; Rouge-Pont et al. 1993). Thus, a positive correlation between novelty-seeking and DA activity in the NAcc, in turn, predicted drug self-administration. This relationship between novelty-seeking and drug self-administration has been demonstrated for amphetamine and cocaine self-administration (Piazza et al. 1989; Belin et al. 2008; Dalley et al. 2007a) but not for MDMA (present results). This might be due to the predominant 5HTergic effects of MDMA.

As described previously, MDMA preferentially increases 5HT (Gough et al., 1991; White et al., 1996; Lyles & Cadet, 2003; Colado et al., 2004; Green et al., 2003) and 5HT was inhibitory to psychostimulant self-administration (Clemens, Cornish, Hunt, & McGregor, 2006; Howell & Byrd, 1995; Peltier & Schenk, 1993; Smith, Yu, Smith, Leccese, & Lyness, 1986; Wee & Woolverton, 2006) possibly via an inhibitory effect on the firing rate of DA neurons in the VTA (Guiard 2008). Thus, it is not surprising that novelty-seeking, which has been linked to DAergic mechanisms, did not predict the latency to acquisition of MDMA self-administration. Instead, the sensitivity to the 5HTergic effects to MDMA and the progression of the 5HT deficit might explain the variability in MDMA self-administration. Interestingly, unpublished findings from our laboratory suggest that acquisition of MDMA self-administration is inversely related to extracellular 5HT in the NAcc. Rats that subsequently acquired MDMA self-administration showed a lower 5HT response to MDMA (3.0 mg/kg MDMA, i.p.). Extracellular DA levels, however, did not differ between rats that subsequently acquired or did not acquire MDMA self-administration. These data support the idea that MDMA self-administration does not depend on an initial sensitivity of DAergic mechanisms, and is therefore different from many other self-administration drugs.

In contrast to novelty-seeking which seems to be mediated by DAergic mechanisms, impulsivity has been associated with reduced 5HT neurotransmission (Harrison et al. 1997a) and thus would be a potential candidate to predict MDMA self-administration. However, impulsivity, as measured in the 5-CSRTT has not been associated with the initial stages of drug-self-administration. Indeed, some studies support the idea that impulsivity in the 5-CSRTT does not reflect the propensity to acquire psychostimulant self-administration (Belin et al. 2008; Dalley et al. 2007a). Rather, impulsivity has been linked to drug-seeking and relapse (Economidou et al. 2009), possibly via activation of a common neural substrate. In the present study, impulsivity failed to explain the latency to acquisition of MDMA self-administration. The possible link via 5HTergic modulation is complicated by the fact that 5HT mechanisms underlying impulsivity in the 5-CSRTT are not yet fully understood. For example, although 5HT depletion increased impulsivity (Harrison et al. 1997a) another study found that increased 5HT neurotransmission in the PFC was positively correlated to impulsive responding (Dalley et al. 2002). Clarification of these contradicting results needs further research but it has been suggested the 5HTergic effects, at least partly, depend on interactions with DAergic substrates. Both, 5HT<sub>2C</sub> antagonists that increase DA neurotransmission and DA agonists increased impulsivity (Fletcher et al. 2007; Winstanley et al. 2004; Higgins et al. 2003; Dalley et al. 2011; van Gaalen et al. 2006). It is possible that this modulatory role of 5HT on DA neurotransmission forms the neurochemical basis for both, increased impulsivity and the progression in MDMA self-administration. Indeed, following chronic MDMA self-administration 5HT neurotransmission became compromised (Schenk et al. 2011a; Do & Schenk 2011) and MDMA produced a sensitized DA response in the dorsal striatum (Colussi-Mas et al. 2010). Thus it has been proposed that the variability in the latency to acquisition of MDMA self-administration might depend on the progression from 5HTergic to more DAergic

mechanisms (Schenk, 2011). A critical test of this idea will be to measure initial and subsequent neurochemical responses to MDMA to determine whether these differences can explain both the impulsivity and self-administration data.

With repeated exposure to drugs of abuse persistent neuroadaptations arise that promote a transition from initial voluntary drug use to compulsive drug-taking and drug dependence. This transition has been proposed to be executed at a neural level from ventral to more dorsal domains of the striatum (Everitt et al. 2008). Low  $D_{2/3}$  receptor availability in the ventral striatum (Dalley et al. 2007a) might promote this transition as it has been shown to be positively correlated to escalating cocaine self-administration as well as impulsivity. As drug-seeking has been shown to produce an enhanced DAergic response in the dorsal but not in the ventral striatum (Colussi-Mas et al. 2010; Ito et al. 2000, 2002) it has been hypothesized that serial processing within the striatum might underlie the progression to drug-seeking.

In one study this hypothesis was tested in disconnecting the ventral from the dorsal striatum (Belin & Everitt, 2008). The NAcc core was selectively lesioned unilaterally combined with contralateral DA receptor blockade in the dorsal striatum. This manipulation functionally disconnects serial interactions between the ventral and dorsal domains bilaterally (Belin & Everitt 2008). Interestingly, this disconnection greatly reduced cocaine seeking in rats which before had shown stable cocaine seeking behaviour in a second-order schedule (Belin & Everitt, 2008). Although the exact mechanisms responsible for this effect are not yet clear, it is an intriguing idea that the low  $D_{2/3}$  receptor availability (possibly in combination with increased drug exposure as expected following the escalation of drug intake) might facilitate this progression of behavioural control to more dorsal domains of the striatum. Impulsivity, thus, might

reflect a neurobiological basis possibly promoting or constraining neuroadaptations caused by repeated exposure to certain substances which might ultimately lead to the development of drug dependence (Koob et al. 1998).

To test and further expand the neural mechanisms underlying this hypothesis seems to be an important target for future research. One possible approach would be to measure DA efflux in the dorsal striatum in high and low impulsive rats prior to and following chronic self-administration. Low  $D_{2/3}$  receptor density in the ventral striatum did not influence basal synaptic DA in the NAcc. Since it has been shown to be predictive of escalating cocaine self-administration it might be possible that low receptor availability had an effect on DA neurotransmission in the dorsal striatum and therefore may contribute to the development of drug-seeking.

Since the level of trait impulsivity depicts a phenotype that predisposes to the propensity to relapse after abstinence (Economidou et al. 2009; Bird & Schenk, 2012) it is further possible that an increase in impulsivity following chronic drug-self-administration could also contribute to the development of drug-seeking behaviour and relapse. This cannot be unambiguously determined in this thesis since it was not possible to assess impulsivity levels in the very early test days following MDMA self-administration, at a time when drug-seeking would have been measured. Typically animals reached the strict extinction criterion preceding drug-seeking tests within 2-3 days but impulsivity levels could only be assessed as early as 5 days following the last self-administration session. It would be interesting to expand the drug-free period beyond 5 days when impulsivity levels have been shown to be increased. Additionally, testing impulsivity concurrently with MDMA self-administration to allow an assessment of impulsive behaviour in early withdrawal stages would, without doubt, provide crucial information. For example, when rats that self-administered cocaine

(morning session) were concurrently tested on the 5-CSRTT (afternoon session) they exhibited an initial but transient increase in impulsive responding. Interestingly, impulsivity increased again during a withdrawal period (Winstanley et al. 2009). It would be interesting to see if MDMA affected impulsivity levels in a similar way and therefore possibly enhanced a drug-seeking response.

The reason why impulsivity could not be measured in the early days following MDMA self-administration was a high number of omission errors which prevented the computation of impulsivity scores. A high level of omitted trials could indicate a motivational or cognitive withdrawal symptom. The effect on omission was not found in the control group suggesting that the effect was not due to the long gap in training.

It is possible to determine a motivational deficit underlying a high number of omitted trials in the standard version of the 5-CSRTT. A motivational deficit would be indexed by a high number of omitted trials and a decrease in the latency to collect the earned reward. In the present study, however, the latency to collect earned reward could not be measured because the food magazine was not equipped with an infra-red beam. Differences in the set up of the 5-CSRTT test chambers (automatic trial initiation in the present study) might in part, account for the high omission rate. In the standard set up, initiation of the next trial is “self-paced” with a nose poke into the food magazine initiating a new trial. Thus, it was not possible in the current study to conclude if the high number of omitted trials was due to an inhibition of motor activity, a deficit in motivation or a cognitive deficit following MDMA self-administration. Nevertheless, there are means to hypothesize about the nature of the observed deficit consulting findings from other studies. In another study measuring 5-CSRTT performance following MDMA self-administration the latency to collect earned reward was initially increased there was no increase in omitted trials (Dalley et al. 2007).

On the other hand, one study from our laboratory suggested impaired memory 7 days following the last MDMA self-administration session that was not due to a motivational deficit. Rats that self-administered MDMA showed no differences in a novel object recognition task (NOR) (Schenk et al. 2011b). In the NOR rats are presented with two identical objects. After a certain exploration period (T1) one of the objects is replaced with a novel object and number of approaches are measured again for another exploration period (T2). A preference for the novel object indicates intact memory function. It is not likely that these findings were due to motivational deficits as MDMA self-administering rats and controls did not differ in their exploratory behaviour towards the two identical objects at T1. It has to be noted that this cognitive deficit was apparent at a time when the performance in the 5-CSRTT had already recovered to control levels. Nevertheless, it is intriguing to assume that withdrawal from MDMA self-administration causes both a motivational and a cognitive deficit, both of which recover over time.

One surprising finding, unrelated to the main objective of the thesis, was that a high percentage of rats that acquired the 5-CSRTT also acquired MDMA self-administration. This effect was not due to an effect of handling, food restriction, or exposure to sweetened condensed milk. One possible explanation of the high acquisition rate is that animals that respond more to reward-paired cues in autoshaping (“sign-tracking”) paradigms are also more likely to approach other reward associated cues. This behaviour is thought to represent individual differences in the attribution of incentive salience to cues, and it has been shown that these rats were more sensitive to cocaine injections and also responded more to a cocaine-paired stimulus (Flagel et al. 2009; Tomie, 1996). These findings suggest that individual differences in the control over behaviour by cues predictive of food rewards may also apply to drug rewards. It is

possible that the acquisition of MDMA self-administration depends in part on these effects and to another part on the individual neurochemical response to MDMA. The strong 5HTergic effects might still delay acquisition but training in the 5-CSRTT might have filtered out a diminishing effect of individual sensitivity to reward-related cues.

When using animal models of human traits or behaviour certain limitations have to be acknowledged. Even the best animal model will never fully replicate a human condition but several aspects of a model are critical. These include reliability (the reproducibility of the results obtained) face validity (the degree of descriptive similarity between, for example, the behavioural dysfunction seen in an animal model and in the human affected by a particular neurobehavioral disorder) and construct validity (the degree of similarity between the mechanisms underlying behaviour in the model and that underlying the behaviour in the condition, which is being modelled).

With respect to novelty-seeking, there are many similarities between sensation seekers and high novelty-seekers. For example, low basal 5HT has been found in both, high sensation seekers and high novelty-seekers (Piazza et al. 1991; Netter et al. 1996) as has an increased DAergic response induced by cocaine or amphetamine (Leyton et al. 2002; Hooks et al. 1991, 1992). Alterations in DA receptors between human and animal studies are consistent and D<sub>2</sub> receptor expression is lower in rats that are high in novelty-seeking and in human sensation seekers (Hooks et al. 1994; Noble et al. 1998). High sensation seekers were more likely to experiment with various illicit drugs (Martin et al. 2002; 2004). They were also more responsive to some drugs of abuse (Leyton et al., 2002; Hutchison et al., 1999; Stoops et al., 2007; Kelly et al., 2006; but see Corr & Kumari, 2000). Accordingly, in the laboratory, rats that were more responsive to novelty showed an enhanced and dose-dependent locomotor response to cocaine injections compared to low responders to novelty (Hooks et al. 1991; Dietz et al. 2005,



2008). Furthermore, animals that show a high response to a novel environment acquired cocaine and amphetamine self-administration with shorter latencies and also self-administered lower doses (Piazza et al. 1989, 2000, Hooks et al. 1991; Marinelli & White 2000; Dalley et al. 2007a; Pierre & Vezina 2007; Belin et al. 2008).

However, sensation seeking in humans predicted ecstasy use (Wu et al. 2010; Martins et al. 2008) but failed to predict MDMA self-administration (present results). This discrepancy might be due to several factors. Firstly, initiation of ecstasy use was defined as at least one occasion on which participants tried at least one ecstasy pill, a behaviour that is hardly comparable to drug-self-administration. Considering that MDMA is an illicit drug and high sensation seekers seem to seek high risk situations in general (taking illicit drugs is a well accepted example of a high risk behaviour), this correlation would not be expected to be explained by a neurobiological mechanism since it occurs prior to drug use. Secondly, ecstasy users usually had experience with other drugs of abuse before they try ecstasy for the first time. It is possible that these drugs have had an effect on subsequent drug taking and the initiation of ecstasy use.

Limitations of animal models of acquisition of drug-taking and drug-seeking also have to be considered when interpreting these results. Differences between the animal model and human use patterns include frequency of dosing and dosage exposure (de la Garza et al. 2007), routes of administration (Ricaurte, 1988), and polydrug use in humans but not by rodents (Cole & Sumnall, 2003).

Finally, impulsivity is a multifaceted phenomenon and is often classified as either impulsive action or impulsive choice. Different procedures have been developed for measurement of these two separate aspects of the trait. A common task that measures impulsive action is the 5-CSRTT used in the present study. On the other hand, impulsive choice is measured using paradigms that require a choice between small and large rewards with temporal variations, which is the basis for delay discounting

procedures. Recent evidence confirmed the independence of these two aspects of impulsivity in laboratory animals using a within subject design to compare the performance in tasks measuring both impulsive action and impulsive choice (Broos et al. 2012). In addition, pharmacological manipulations have shown dissociable effects on impulsive action and impulsive choice, suggesting independent neural circuits (Broos et al. 2012). These various tasks further require behavioural inhibition at different points in the response process (e.g. choice processing, response preparation, initiation of behaviour or action cancellation, Dalley et al. 2011). Thus, impulsive action and impulsive choice can be differentiated at a behavioural as well as a neural level. Indeed, impulsive choice has been associated with the acquisition of cocaine self-administration (Perry et al.; 2005, 2008) and it would be of interest to see if there is a similar relationship with MDMA self-administration.

This study is the first to describe the contribution of two psychobiological traits to MDMA self-administration. The present findings suggest some implications for the prevention and treatment of drug dependence.

Impulsivity has been suggested to be a risk factor for psychostimulant addiction and the present results strengthen this idea. In fact, this is the first study to link trait impulsivity to MDMA self-administration, in particular to MDMA induced drug-seeking. Impulsivity levels were increased following chronic drug exposure and this increase might contribute to a higher propensity to relapse. These findings highlight the importance of considering psychobiological traits in the development of addiction treatment options. In particular, relapse prevention treatment might benefit from employing pharmacological and psychological strategies aiming to reduce impulsive behaviour as well as to prevent drug-seeking.

The findings of the present thesis also trigger some intriguing questions for future research. In particular, there are two lines of research worth following. First, further research examining neurobiological factors mediating impulsive behaviour is crucial for understanding its effects on drug-self-administration. An important avenue for investigations is the interplay between 5HT and DA substrates. Second, mechanisms underlying MDMA self-administration need further examination. In particular, identification of neural mechanisms underlying the acquisition of self-administration is critical. The measurement of the neurochemical response to MDMA in drug-naïve and experienced rats might be valuable. A crucial experiment would be to measure the neurochemical response to MDMA in drug-naïve and experienced rats following MDMA and cocaine self-administration, as prior training with cocaine facilitated the acquisition of MDMA self-administration (Schenk et al. 2003). This effect has been hypothesized to be due to an enhanced DAergic sensitivity. Furthermore, determination of the role of the 5HT deficit following MDMA self-administration will be important.

The possibility that impulsivity might have predicted the propensity for self-administration to escalate with longer duration sessions is worth testing. One means of addressing this question would be to quantify response patterns during the maintenance phase of self-administration following more extensive exposure to self-administered MDMA. This escalated drug-taking might in turn facilitate neuroadaptions that consequently lead to compulsive drug seeking and dependence.

## **V. Conclusions**

The present study suggests that novelty seeking does not predict either latency to acquisition of MDMA self-administration or drug seeking following extensive experience with MDMA self-administration. Because impulsivity and novelty seeking were not correlated, these two traits might be expected to be related to different aspects of self-administration, as has been suggested by previous studies (Belin et al. 2008; Dalley et al. 2007a). The failure to observe a relationship between novelty seeking and acquisition of MDMA self-administration might reflect differences in the substrate mediating the initial response to MDMA (5HT) and novelty seeking (DA). Impulsivity also failed to predict latency to acquisition of MDMA self-administration but was positively correlated with the MDMA-produced potentiation of drug seeking.

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