# Comparison of Methamphetamine and MDMA Extended Access Self-administration: Acquisition, Maintenance, and Response patterns

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## Abstract

*Rationale*. 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine are two amphetamine derivatives with contrasting pharmacological profiles. Therefore, self-administration profiles might be expected to reflect these differences.

*Objectives.* This study compared the latency and proportion to acquire self-administration, maintenance of self-administration, and within-session response patterns.

Methods. Rats were given extended access (8-hour daily sessions) to either methamphetamine, MDMA or vehicle self-administration over a period of 10 consecutive days. A criterion based on the performance of the vehicle control group was used to determine acquisition of reliable MDMA and methamphetamine self-administration. In conjunction, for MDMA self-administration the infusion dose was halved for each rat that achieved a total of 85mg/kg for the remaining sessions. Temporal patterns of responding were assessed using hourly data of the first day of self-administration, the day following acquisition, and the final day of self-administration.

*Results.* A greater proportion of rats in the methamphetamine group acquired self-administration and self-administration was acquired with a shorter latency compared to the MDMA group. Responding maintained by methamphetamine on day one was high. By the third day a pattern developed that was maintained throughout testing. The greatest proportion of responding occurring within the first hour of each daily test session. A progressive escalation of intake was also observed within the methamphetamine group. Responding maintained by MDMA was low on the first day, but by day 5 responding had increased with most of the responding within the session occurring during the first three hours. On day 10 the greatest amount of responding occurred during the first hour. No escalation of intake as a function of test day was observed for MDMA self-administration.

*Conclusions.* These findings suggest some differences in the acquisition and maintenance of methamphetamine and MDMA self-administration. In the case of methamphetamine, we suggest neuroplastic adaptations contributed to the gradual increase of intake following acquisition of self-administration, and for MDMA, we suggest the neuroplastic adaptations likely facilitated the acquisition of self-administration.

# Introduction

## Substance Use Disorder

A substance use disorder (SUD) is a chronic relapsing disorder characterised by a maladaptive pattern of substance use, including a progressive increase in drug use, cravings, and persistent use despite adverse consequence or desire to abstain (APA, 2013). For those who develop SUDs, treatment options are limited, and relapse is common even after treatment and/or extended periods of abstinence (DeJong, 1994; Sayette, 2016; Brecht & Herbeck, 2014). The pharmacological effects of drugs that are relevant to their misuse have therefore been investigated with the hopes of providing improved treatment outcomes.

## The Role of Dopamine

Drugs of abuse can have varying primary pharmacological effects, however, almost all drugs that are misused increase mesolimbic dopamine (DA) transmission either directly or indirectly (Wolf, 2002). The acute reinforcing properties of psychostimulant drugs have been attributed to these dopaminergic mechanisms (Koob and Volkow, 2010).

Drug naïve subjects were administered intravenous (IV) cocaine or an equipotent dose of methylphenidate, both of which are dopamine transporter (DAT) inhibitors that increase synaptic DA. Each drug was labelled with carbon-11 and positron emission tomography (PET) was used to assess DAT receptor binding in the striatum (For DAT occupancy calculations see Volkow et al., 1997a) and subjective/self-report measures of ‘high’ and ‘euphoria’ were collected. A subjective ‘high’ was only reported when approximately 50% of DAT was occupied, and the perceived level of ‘high’ increased as a function of DAT blockade (Volkow et al., 1997a).

A follow up study assessed striatal $D_2$ binding as a correlate of methylphenidate-induced DA release. This was achieved using the radioligand [$^{11}$C]raclopride which competes with endogenous DA for $D_2$ receptor binding. This required two PET scans, one after administration of [$^{11}$C]raclopride and a placebo, another after administration of [$^{11}$C]raclopride and methylphenidate. The relative difference between $D_2$ binding from each scan was then used as a measure of methylphenidate induced DA and was correlated with the self-report measure of 'high'. Consistent with DAT binding, self-reported 'high' increased as a function of $D_2$ receptor binding. Further, those who did not perceive a 'high' exhibited no change in striatal $D_2$ binding (Volkow et al., 1999). Together, these data demonstrated a relationship between the role of DA and the acute reinforcing properties of psychostimulants (Volkow et al., 2002).

However, while this supports a role of DA plays in the rewarding effects of drugs of abuse, it fails to explain why only some users develop an SUD (Nutt et al., 2007; Uhl and Grow, 2004; Volkow et al., 2002). It is likely that drug-induced neuroadaptations occur as a consequence of repeated drug exposure that may contribute to the development of SUD as discussed below. One focus of neuroimaging studies has been to compare $D_2$ receptor binding of healthy controls and those with a history of drug misuse. A reduction in striatal $D_2$ has been observed in subjects with an extensive history of cocaine (Volkow et al., 1993), alcohol (Volkow et al., 2006), methamphetamine (Lee et al., 2009), heroin (Martinez et al., 2012) and nicotine (Fehr et al., 2008) misuse.

A decrease in $D_2$ receptor binding has been attributed to a blunted reward response to both natural reinforcers and drugs of abuse (Volkow, 1997b). For example, previous cocaine users reported less positive subjective effects following administration of IV methylphenidate as compared to healthy controls (Volkow, 1997b). One might think a reduction in the rewarding effects of drugs of abuse may lead to the cessation of their consumption, however,

this does not appear to be the case. It is possible that a decrease in responsivity to drugs of abuse results in a compensatory increase of drug-intake, and indeed this has been extensively documented (Volkow et al., 2004). Consistently, the diagnostic criteria in the DSM-V includes an increase in drug consumption (both in frequency and quantity) and tolerance to the drugs effect, among other things (APA, 2013).

DAergic markers have also been measured post-mortem following drug misuse. Chronic methamphetamine users showed a marked reduction in tissue levels of DA, tyrosine hydroxylase (the rate-limiting enzyme for DA and norepinephrine (NE) synthesis), DAT within the striatum - in particular the caudate nucleus (McCann et al., 1998, 2008; Sekine et al., 2001; Moratalla et al., 2014), and DA $D_2$ receptors (Wilson et al., 1996). Interestingly, $D_1$-like receptor expression was elevated in the terminal regions of the mesolimbic DA system (the nucleus accumbens; NAc) of heavy methamphetamine users and might also contribute to continued methamphetamine use (Worsley et al., 2000). Similar methamphetamine-induced neuroplastic changes have also been observed outside of the striatum, including the prefrontal cortex (Chang et al., 2007; Sekine et al., 2001). Users who remained abstinent showed a partial but not full recovery of many of these DAergic markers (McCann et al., 1998; Volkow et al., 2001; Marshall and O'Dell, 2012).

Neuroimaging techniques are unable to directly measure synaptic release of neurotransmitters, but this can easily be achieved in laboratory animals via placement of an intracranial dialysis probe. DA overflow within the NAc was assessed in freely moving rats following subcutaneous (SC) administration of drugs that are misused by humans including amphetamine, cocaine, morphine, ethanol and nicotine. Increases of 1000%, 330%, 200%, 190%, and 220%, respectively, were observed (Di Chiara and Imperato, 1988). Furthermore, drugs that are not misused such as antidepressants failed to increase synaptic DA (Di Chiara and Imperato, 1988).

This role of DA in substance misuse has been extensively investigated in preclinical studies of self-administration (Rothman and Glowa, 1995). During these studies, rats, and other laboratory animals, are fitted with intravenous catheters for drug infusions. Performance of an operant (a lever press or nose poke for example) provides an infusion of a drug (see below for more procedural details). A large number of studies have demonstrated the important role of DA in this self-administration behaviour.

DA transporter inhibitors (Lile et al., 2004), as well as $D_1$-like and $D_2$-like receptor agonists (Ranaldi et al., 2001; Self and Stein, 1992; Weed and Woolverton, 1995; Woolverton et al., 1984) maintained responding when substituted for cocaine or amphetamine after the acquisition of self-administration of these drugs (Ranaldi et al., 2001; Weed and Woolverton, 1995; Woolverton et al., 1984) and were also self-administered by drug naïve laboratory animals (Howell and Byrd, 1991; Nader and Mach, 1996; self et al., 1996; Self and Stein, 1992; Wee and Woolverton, 1995; Yokel and Wise, 1978). Furthermore, pharmacological manipulations of DA shifted the dose-effect curve in a predictable manner. For example, DA receptor antagonists dose-dependently increased responding maintained by cocaine, amphetamine, and methamphetamine, suggesting a compensatory increase in responding due to blockade of these receptors and a rightward shift in the dose-effect curve (Caine and Koob, 1994; Caine et al., 1995; Barrett et al., 2004; Bari and Pierce, 2005). DA agonists decreased responding maintained by cocaine (Caine et al., 1995) and alcohol (Rassnick et al., 1993) suggesting a leftward shift to the dose-response curve. Neurotoxic 6-hydroxydopamine (6-OHDA) lesions localized to NAc or to the cell body regions in the ventral tegmental area (VTA) attenuated nicotine (Corrigall and Coen, 1991), cocaine (Pettit et al., 1984; Roberts and Koob, 1982) and amphetamine (Lyness et al., 1979) self-administration, and blocked the acquisition of ethanol (Ikemoto et al., 1997) and heroin self-administration (Bozarth and Wise, 1986).

**Methamphetamine**

Like many other drugs of abuse, the high abuse liability of methamphetamine has been attributed to an increase in synaptic DA (Baumann et al., 2002). This is achieved through the reversal of the DAT whereby extracellular methamphetamine is exchanged for intracellular DA, and further mediated through the reversal of VMAT2, leading to the displacement of vesicular DA to the extravesicular cytosol (Sulzer et al., 2005).

The role of DA in methamphetamine self-administration has been investigated using a variety of DA receptor ligands. Pre-treatment with non-selective DA agonists decreased methamphetamine self-administration (Munzar et al., 1999; Reichel et al., 2008), suggesting a leftward shift in the dose-effect curve. $D_1$-like receptors antagonists also dose-dependently decreased responding maintained by methamphetamine in rats, although this has been attributed to a rightward shift in the dose-effect curve (Brennan et al., 2009). In contrast, $D_2$-like antagonists failed to produce an effect (Brennan et al., 2009). The partial $D_2$ receptor agonist, aripiprazole, decreased methamphetamine maintained responding and reduced the motivation to self-administer methamphetamine as measured using a progressive ratio schedule (Wee et al., 2007). Furthermore, the $D_3$ receptor antagonist, SB-277011A, also decreased methamphetamine self-administration (Higley et al., 2011). Inhibition of VMAT2 via lobelane prevented methamphetamine-induced DA release (Nickell et al., 2010), and reduced methamphetamine self-administration (Neugebauer, 2007). These data suggest that DAergic mechanisms are involved in the reinforcing effects of methamphetamine, with $D_1$-like mechanisms being primarily responsible for self-administration (Brennan et al., 2009).

Methamphetamine is also a full agonist of the trace amine associated receptor 1 (TAAR1) which acts as a monoaminergic modulator (Rutigliano et al., 2018; Xie et al., 2008). Repeated activation of TAAR1 by methamphetamine induces the internalisation of DAT (Xie et al., 2008). Pre-treatment with the TAAR1 partial agonist RO5203648 attenuated

methamphetamine-induced striatal DA release and reduced methamphetamine reinforced responding (Cotter et al., 2015). Consistently, the full TAAR1 agonist RO5263397 produced a similar decrease in methamphetamine self-administration (Jing et al., 2015).

Chronic methamphetamine use produces neuroplastic adaptations, most prominently deficits within DAergic markers and have been well documented in both humans (Lee et al., 2009; McCann et al., 1998, 2008; Sekine et al., 2001, Wilson et al., 1996) and laboratory animals (Kransnova et al., 2010; Ricaurte et al., 1980; Schwendt et al., 2009; Shepard et al., 2006; Stefanski et al., 1999; Seiden et al., 1976, 1977; Wollverton et al., 1989). These adaptations are thought to underlie the severe cognitive and behavioural deficits present in heavy methamphetamine users (Simon et al., 2000, 2002; Newton et al., 2004; Rendell et al., 2009), and contribute to the development of a methamphetamine SUD (Parsegain and See, 2014).

The persistence of methamphetamine-induced neuroadaptations has also been demonstrated in rats (Kransnova et al., 2010; Ricaurte et al., 1980; Schwendt et al., 2009; Shepard et al., 2006; Stefanski et al., 1999) and non-human primates (Seiden et al., 1976, 1977; Wollverton et al., 1989). Similar methamphetamine-induced neuroplastic changes have also been observed outside of the striatum, including the prefrontal cortex (Chang et al., 2007; Sekine et al., 2001).

**MDMA**

In contrast to the well-documented role of DA in methamphetamine and other stimulant self-administration, a role in (+-)3,4-methylenedioxymethamphetamine (MDMA) self-administration has been studied to a lesser extent. MDMA is also an amphetamine derivative and is the primary active ingredient in the street drug ‘ecstasy’. It produces positive subjective effects of euphoria, increased sense of closeness, increased sensory

awareness, and elevated confidence (Liechti et al., 2001; Tancer and Johnson, 2003; Vollenweider et al., 2001). MDMA is not often considered a drug of abuse but some users met the DSM criteria for an SUD (Degenhardt et al., 2010; Hanson and Luciana, 2004; Jansen, 1999; Parsons et al., 2009; Schifano and Magni, 1994; Schuster et al., 1998; Topp et al., 1997; Yen et al., 2007; Hopper et al., 2006; McKetin et al., 2014).

Unlike methamphetamine and other drugs of misuse, acute administration of MDMA preferentially increases synaptic levels of serotonin (5HT) due to a high affinity for the 5HT transporter protein (SERT) (Berger et al., 1992; Fitzgerald and Reid, 1990; Gough et al., 1991; Johnson et al., 1986; Nash and Brodkin, 1991). Reversal of SERT occurs through the facilitated exchange of extracellular MDMA for intracellular 5HT. Furthermore, this exchange induces a change in cytosol pH which subsequently induces the movement of vesicular 5HT down the gradient to the cytoplasm where it becomes available for release (Rudnick and Wall, 1992). Approximately 80% of available 5HT can be released into the synapse following an acute dose (Green et al., 1995; 2003).

Acute exposure to MDMA also increases synaptic DA, albeit to a lesser extent than 5HT. However, a high dose of MDMA enhanced synaptic levels of DA that were comparable effects produced by other amphetamines (Cadoni et al., 2005; Kalivas et al., 1998; O'Shea et al., 2005; Shankaran and Gudelsky, 1999; Baumann et al., 2008a; Nair and Gudelsky, 2004; Schmidt et al., 1994.

Drug-induced increases in synaptic 5HT are generally inhibitory to self-administration (Rothman and Baumann, 2006). For example, the magnitude of self-administration was inversely related to SERT affinity (Ritz and Kuhar, 1989), and 5HT agonists (Collins et al., 2016; Cunningham et al., 2011; Howell and Byrd, 1995; Miszkiel et al., 2012), 5HT releasers (Munzar et al., 1999), and SERT inhibitors (Carrol et al., 1990; Howell and Byrd, 1995) attenuated psychostimulant self-administration. Consistently, 5HT

antagonists enhanced the effects of stimulants (Howell and Byrd, 1995; Miszkiel et al., 2012).

It may seem then MDMA would not support reliable self-administration due to preferential 5HTergic effects, but this is not the case. While less animals tend to acquire MDMA self-administration and latency to acquisition is protracted compared to self-administration of other stimulants such as cocaine (Schenk, 2003), for those that do (approximately 60%) high rates of responding are maintained (Schenk et al., 2007; Schenk et al., 2008; Colussi-Mas et al., 2010; Schenk et al., 2011; Schenk et al., 2012; Schenk et al., 2016). This may result from a change in the pharmacology of MDMA following repeated exposure. Following repeated exposure to high doses of MDMA, there were marked reductions in SERT density in the cerebral cortex, striatum, and thalamus (Battaglia et al., 1991; Mamounas et al., 1991; O'Hearn et al., 1988; Scanzello et al., 1993; Ricaurte et al., 1987, 1988). Damage to these neuronal populations was persistent (Doherty and Pickel, 2001; Battaglia et al., 1987; Commins et al., 1987; Lyles and Cadet, 2003; Schmidt, 1987; Sprague et al., 1998; Stone et al., 1987), and similar persistent 5HT deficits were also apparent in abstinent MDMA users (Cowan, 2007; Kish et al., 2010; McCann et al., 2008; Reneman et al., 2006; Erritizoe et al., 2011; Benningfield and Cowan, 2013). It has been suggested that these deficits underlie the progressive increase in MDMA self-administration (Schenk, 2011) because of disinhibition of MDMA-produced DA (Alex and Pehek, 2007).

Manipulations of 5-HT have supported this idea. Genetic deletion of SERT in rats facilitated MDMA self-administration suggesting an increased sensitivity to the rewarding properties of MDMA (Oakly et al., 2014). Destruction of 5-HT terminals via 5,7-dihydroxytryptamine (5,7-DHT) lesions produced a similar effect (Bradbury et al., 2013). Furthermore, a down-regulation of $5HT_{1a}$ and $5HT_{1b}$ receptors resulting from repeated exposure to the $5HT_{1a/1b}$ receptor agonist RU 24969 also facilitated the acquisition of MDMA

self-administration (Aronsen et al., 2016). 5HT antagonists ($5HT_{1a}$, $5HT_{1b}$, $5HT_{2a}$) failed to alter MDMA self-administration (Schenk et al., 2016) supporting the idea that other neural mechanisms must be involved.

A role of both DA $D_1$-like and $D_2$-like receptor mechanisms in MDMA self-administration has been demonstrated. The $D_1$-like antagonist, SCH 23390, or the $D_2$-like antagonist, eticlopride, shifted the dose-effect curve for MDMA self-administration to the right (Daniela et al., 2004; Brennan et al., 2009). Similarly, intracranial (IC) self-administration of MDMA directly into the NAc shell was blocked by co-administration of $D_1$-like and $D_2$-like antagonists (Shin et al., 2008).

These data support the idea that DA is critical for both MDMA and methamphetamine self-administration. There may, however, be different roles of DA receptor subtypes with both receptor subtypes being involved in MDMA self-administration but $D_1$-like receptors being more critical for methamphetamine self-administration.

**Comparison of Methamphetamine and MDMA**

While both are amphetamine analogues, methamphetamine and MDMA have different pharmacological profiles, at least following acute administration (Baumann et al., 2002, 2005, 2008). However, repeated MDMA exposure produced selective deficits in 5HT neurotransmission and it has been suggested that these deficits might contribute to the acquisition of MDMA self-administration (Aronsen et al., 2016; Bradbury et al., 2014; Highgate and Schenk, 2018; Oakley et al., 2014; Schenk, 2011). Methamphetamine exposure can also produce deficits in 5HT neurotransmission (Volz et al., 2007), but 5HT does not appear to play a prominent role in methamphetamine self-administration. For example, genetically manipulated mice missing the tryptophan hydroxylase gene (these mice have no central 5HT) exhibited no differences in methamphetamine-maintained responding compared

to wild type mice (Thomas et al., 2010). This is likely due to the limited release of methamphetamine-induced 5HT (Jaehne et al., 2017).

If, in fact, the self-administration of both drugs becomes dependent on the same DAergic mechanisms, then the profile of self-administration would be expected to be comparable. Such an assessment must also take in potential differences in pharmacokinetic profiles. Methamphetamine is relatively short-acting in rats with a half-life less than 1 hour (Melega et al., 1995; Rivière et al., 2000), while racemic MDMA has a half-life between 2 and 3 hours in rats (Bradbury et al., 2014; Fonsart et al., 2009). Self-administration tends to occur as DA levels of the drug fall below a threshold (Wise et al., 1995). Accordingly, the temporal pattern of self-administration for MDMA might be expected to initially differ from the pattern of self-administration of methamphetamine because of high levels of MDMA-produced 5HT release (Alex and Pehek, 2007), but as MDMA induced 5HT deficits occur, responding may become more similar as MDMA-DA release becomes more prevalent. A comparison of response rates and the temporal pattern of responding maintained by these two drugs during acquisition and maintenance of self-administration is the focus of this thesis. An important consideration for such a comparison is the self-administration protocol used. A brief history and justification for the protocol adopted is provided below.

**Self-administration**

A prototypical rodent self-administration (SA) study is conducted using chambers equipped with two levers, a stimulus light, and an infusion pump. Depression of one lever (active) results in a subsequent drug infusion and concurrent illumination of the stimulus light. Depression of the second lever (inactive) is recorded but typically has no programmed consequence. A range of animals including non-human primates have been subjects of SA studies, however rodents such as rats and mice are most commonly used and quickly learn to

self-administer most classes of drugs that are misused by humans (Caine et al., 1993; O'Connor et al., 2011, Olmstead, 2011).

Drug infusions are typically paired with a discriminative stimulus, such as a light. Through the process of Pavlovian conditioning, the light stimulus gains conditioned reinforcing properties and becomes capable of driving behaviour in the absence of the primary drug reinforcer (Ciano and Everitt, 2004; Daniela et al., 2006). Conditioned reinforcers add salience and can also facilitate responding maintained by drug infusions (Daniela et al., 2006; Kruzich et al., 2001; Leshner, 1998; Robinson and Berridge, 1993; Panlilio et al., 2000; See et al., 1999). Drug-associated stimuli can both signal the availability of the drug, and illicit the conditioned response of craving (Hartz et al., 2001; Killen and Fortmann, 1997; Shulman, 1989; Wallace, 1989). The magnitude of control drug-associated stimuli on behaviour can be considered an index of substance misuse (O'Brien et al., 1998; Wikler, 1973).

The amount of responding maintained by self-administration is dependent on the schedule of reinforcement, pharmacological profile, session duration and dose among other things (Ahmed, 2012). Session duration, in particular, has recently been manipulated in an attempt to provide a more ecologically relevant model of substance misuse (Ahmed and Koob, 1998).

Historically self-administration studies used sessions that were rather short in duration – approximately 1-2 hours. Under these conditions acquisition was rapid (depending on dose) and the response rates produced were high. Following the initial acquisition phase, the rate of responding across sessions tended to remain remarkably stable with little individual variation over time (Ahmed, 2011, 2012; Edwards and Koob, 2013). It was not until decades later that this was suggested to pose a problem to the validity of self-administration as a paradigm to study SUDs. It was suggested that the consistent and regulated pattern of self-administration

produced under short access conditions did not reflect the shift to uncontrollable use apparent in humans (Ahmed, 2012; Deroche-Gamonet and Piazza, 2004).

**Shift from short access to long access self-administration**

The basic procedure of the self-administration paradigm has recently been modified in numerous ways to investigate specific aspects of SUD such as the transition from controlled to uncontrollable use, relapse, and continuing to administer drugs despite adverse consequence (Ahmed, 2012). When provided extended access to drugs of abuse a range of behavioural changes that are theorized to better model substance misuse is produced when compared to effects produced following short access conditions.

In particular, the use of longer-duration self-administration sessions produces a progressive escalation of intake that is not produced when shorter duration sessions are employed (Koob and Le Moal, 1997; Ahmed, 2012; Benowitz and Henningfield, 1994). This compares favourably with the controlled use exhibited by cocaine users that did not meet the criteria for an SUD compared to those with an SUD (Pottieger et al., 1995). It has been suggested that prolonged exposure to elevated blood levels are necessary, or at least exacerbate, drug-induced neuroadaptation (Davidson et al., 2001; Gawin and Ellineood, 1989; Kramer et al., 1967; Nordahl et al., 2003; Meredith et al., 2005; Roberts et al., 2002; Robinson and Berridge, 2008; Rogers et al., 2008; Simon et al., 2001), and contribute to an escalation of intake and uncontrolled use characteristic of an SUD (Zimmer et al., 2012).

In the seminal study, two groups of rats were given access to cocaine self-administration; one group for 1 hour per day, the second group had 6 hours of access per day. As expected, both groups acquired self-administration of cocaine rapidly. Importantly, following acquisition responding within the short access group remained incredibly stable across days, while responding for the extended access group progressively increased as a

function of day. During extended access conditions there was an overall upward shift in the entire dose-effect curve and more responding during the first hour. The effect of session length was restricted to self-administration since the two groups did not differ in the magnitude of cocaine-induced hyper-locomotor activity. This suggests that an escalation of drug intake across sessions does not simply reflect tolerance or sensitisation to the drug, but rather an upward shift in hedonic set point (Ahmed and Koob, 1998; Ben-Shahar et al., 2004; Berridge and Robinson, 1998; Berridge, 2012; Flagel et al., 2009; Koob et al., 2004).

An escalation of intake following long-duration sessions has been demonstrated for self-administration of a range of substances including methamphetamine (Ahmed, 2005; Kitamura et al., 2006; Hadamitzky et al., 2011, 2012), heroin (Ahmed et al., 2000), MDMA (Highgate and Schenk, 2018 Van de Wetering and Schenk, 2019), and methylphenidate (Marusich et al., 2010).

Extended access to methamphetamine produced dose-dependent rates of escalating intake (Kitamura et al., 2006). When the dose of methamphetamine was low (0.05mg/kg/infusion) approximately 3.0mg/kg total was administered during the first session and intake gradually increased over a period of 15 days after which daily intake plateaued at 9.0 mg/kg and remained stable for a further 6 days of testing. In contrast, when a high dose was self-administered (0.2mg/kg) intake was 6mg/kg during the first session, increased to 9 mg/kg after 6 days of testing and remained stable for a further 15 days of testing. These findings show that a more potent dose of methamphetamine can result in greater initial intake, and a more rapid escalation of intake across days, while a lower dose may produce a more gradual escalation of intake that is greater in magnitude. Regardless of dose, the escalation of intake was most pronounced within the first hour of responding as is consistent with other drugs of abuse (Ahmed and Koob, 1998, 1999, 2005; Ahmed et al., 2000, 2002, 2003; Ben-Shahar et al., 2004; Highgate and Schenk, 2018).

Under long access conditions to MDMA an escalation of intake as a function of days was also observed (Highgate and Schenk, 2018; van de Wetering and Schenk). Upon meeting acquisition criterion, approximately 15mg/kg was self-administered throughout the session. This increased to approximately 40 mg/kg by the final day of testing. As with methamphetamine (Kitamura et al., 2006), this increase in intake occurred predominantly within (but not limited to) the first hour of responding.

The escalation of intake was associated with an increased motivation to self-administer drugs of abuse as indicated by an increase in breakpoint during a progressive ratio schedule of reinforcement (Allen et al., 2007; Larson et al., 2007; Wee et al., 2007, 2008; Orio et al., 2009, Hao et al., 2010; Lenoir and Ahmed, 2008). This might be comparable to behaviour exhibited by those with an SUD who engage in the often excessive and effortful process of seeking out a drug when it is not readily available, compared to casual users who are only likely to consume the drug when it is readily available (Anthony, 2002; Swendsen and La Moal, 2011). This increase in motivation produced by extended access conditions is thought to be at least partly responsible for the escalation of intake (Deroche-Gamonet et al., 2004).

Other characteristics of an SUD are also produced following long access self-administration conditions. For example, those with SUD will continue to use drugs despite adverse consequences, like bad health and loss of social function (Volkow et al., 2011). In laboratory animals this can be modelled by altering the self-administration procedure to add a reward contingent punisher (such as a foot shock) after acquisition of the initial self-administration behaviour. Compared to rats given limited drug access, extended access resulted in resistance to the effects of punishment (Ahmed, 2011), or the presence of punishment signalling cues (Vanderschuren and Everitt, 2004) on self-administration.

Additionally, relapse to drug use is high with approximately 60% of those with an SUD relapsing within their lifetime (McLellan et al., 2000). Relapse is often initiated by intense cravings that are elicited by a stress response, acute exposure to the drug, or conditioned cues such as drug related paraphernalia and interoceptive context (Furguson and Shiffman, 2009).

Cravings can be assessed by using well validated questionnaires, however a different approach is required for laboratory animals. Latency to extinction of self-administration when the drug solution is replaced with an inert substance is one measure of drug-seeking that has been used to examine relapse potential (Ahmed et al., 2000). Extended access conditions produced resistance to extinction of this measure of drug-seeking (Ahmed et al., 2000). This is true for even detoxified rats implying that this drug-seeking is not to alleviate withdrawal symptoms, but rather a compulsive urge to engage in drug use. It has been sown that following long duration cocaine or methamphetamine self-administration sessions drug-seeking was persistent (Ahmed, 2012; Grimm et al., 2001; Dalley et al., 2007; Ferrario et al., 2005; Rogers et al., 2008).

Following extinction of drug-seeking, the presentation of a stimulus that had been associated with self-administered drugs, stress, or an acute experimenter administered injection of the drug reinstated the extinguished response (Epstein and Preston, 2003). Rats with a history of extended access to self-administered cocaine exhibited an increase in drug-seeking responding compared to their short access counterparts (Ahmed and Cador, 2006; Kippin et al., 2006; Knackstedt and Kalivas, 2007; Mantsch et al., 2004, 2008).

Because of the demonstrated validity of long duration self-administration sessions in terms of modelling some of the characteristics of an SUD, this thesis will use only long access self-administration conditions. The main question to be addressed is whether the profile of methamphetamine and MDMA self-administration under these conditions is

comparable or not. The measure was the change in the temporal pattern of responding during these long access self-administration sessions.

**Patterns of responding in self-administration**

While most self-administration studies report total number of responses per session, others have attempted to describe the temporal pattern of responding within a session. Although less change in behavioural output is observed within short duration sessions, longer access sessions typically involve two phases of responding; a loading phase and a maintenance phase (Ettenberg et al., 1982; Wilson et al., 1971).

The loading phase occurs at the beginning of each session (the first 30 minutes – 1 hour) when blood levels of the drug are initially zero. This phase is characterised by high levels of responding (short inter-infusion intervals) that result in a rapid spike of drug blood levels. Following this there is a maintenance phase during which responding is characterised by long and regular inter-infusion intervals that are evenly spaced in order to maintain elevated blood levels of the drug.

The amount of responding within each phase is impacted by the pharmacological profile of the drug including the potency to increase synaptic DA as well as pharmacokinetic factors (Tsibulsky and Norman, 1999). For example, a high dose of a drug will increase synaptic DA more rapidly with fewer responses compared to when a lower dose is self-administered (Pettit and Justice, 1989, 1991; Wise et al., 1995),. Furthermore, the duration of drug elicited DA is governed by the pharmacokinetic profile of a drug, which in turn dictates the response rate during the maintenance phase (Wise et al., 1995). For example, a drug such as cocaine that has a very short elimination half-life produces self-administration with short inter-infusion intervals as compared to a drug with a longer elimination half-life such as

amphetamine that produces self-administration with longer inter-infusion intervals (Panlilio et al., 2003).

A stimulus control hypothesis has been used to explain the pattern of self-administration (Panlilio et al., 2007). According to this account, the effect of the drug serves as an interoceptive cue that signals the level of reinforcement received by an injection. For example, dialysate levels of DA in the NAc predicted self-administration; responding was produced when DA levels fell below a threshold (Wise et al., 1995). Therefore, it was suggested that drug elicited NAc DA served as an index for responding (Panlilio et al., 2007).

Due to differences in pharmacological profiles, such as differences in neurotransmitter release, drug-induced neuroadaptations, and pharmacokinetics it would be of interest to compare patterns of responding maintained by MDMA and methamphetamine. Because MDMA initially produces a preferential increase in 5HT, self-administration is expected to be limited. However, as MDMA induced 5HT deficits occur, a DA response is theorised to become disinhibited (Schenk, 2011), and consequently the temporal patterns of responding maintained by MDMA might come to resemble that of methamphetamine. However, there are still differences in DA receptor contribution (most notably $D_2$-like receptors) so it is also possible that differences in responding may persist and contribute to differences in the profile of self-administration of the two drugs. This had yet to be compared, and therefore was the purpose of the current study.

Under long access conditions amphetamines such as MDMA and methamphetamine show a distinct loading phase followed by a maintenance phase. During 2-hour daily MDMA self-administration sessions higher doses were primarily self-administered within the first 30 minutes of each session whereas lower doses were self-administered throughout the session (Schenk et al., 2003). Regardless of dose, intake was maintained at approximately 20mg per

session. However, when given 24-hour access to MDMA (1.0 mg/kg) a loading phase was demonstrated and was characterised by high responding which was followed by a maintenance phase with approximately 2-4 responses per hour (Schenk et al., 2003). The same lab (Highgate and Schenk, 2018) found that after extensive experience approximately 40% of responding occurred within the first hour. Furthermore, responding during hours 2-6 was approximately 10 responses per hour which were comparable in regard to intake (mg/kg) when compared to 24-hour access (Schenk et al., 2003).

The low level of responding during the maintenance phase was attributed to the long duration of action of MDMA and the associated metabolites (Schenk, 2003). Most importantly, during extended access conditions there was a gradual increase in MDMA-maintained responding as a function of day. Interestingly, this escalation of intake occurred during the first hour of responding, while responding from hours 2-6 increased to a lesser extent (Highgate and Schenk, 2018). Together these findings suggest that during extended access to MDMA there are distinct loading and maintenance phases. Furthermore, the escalation of intake occurs within the loading phase which may reflect an increase in hedonic set point.

Temporal patterns of responding maintained by methamphetamine were first assessed in rats in 1967 (Pickens et al., 1967). During the initial days of unlimited access to self-administration responding was low and irregular. However, responding escalated by the fourth day responding stabilized and inter-infusion intervals were regular. Periods of responding lasted between 24-48 hours and were separated by periods of inactivity that typically lasted between 12-24 hours. Interestingly, no loading phase was reported in this initial study although this was likely due to the use of a large dose (0.5mg/kg), furthermore, the 4-day escalation of intake likely reflected acquisition of self-administration as no changes

in response patterns were reported for the following four weeks. This could have been due to the extremely high dose used, or the long infusion time of 50 seconds.

Not until over three decades later was self-administration of methamphetamine assessed again in rats (Munzar et al., 1999). Access to a much lower dose of methamphetamine (0.06mg/kg) was available during 2-hour sessions, 5 days per week. After responding stabilized (responding did not vary more than 20% over 5 consecutive sessions) the temporal pattern of responding was measured. The session was divided into four 30-minute segments (0-30, 30-60, 60-90, 90-120). Under these conditions, the highest amount of responding occurred within the first 30-minute segment with approximately 13 infusions. A progressive decrease in responding was observed across the remaining three segments, however the greatest drop in responding was between the first and second segments which usually halved (approximately) in the number of responses. This appears to suggest a distinct and relatively short loading phase during low dose methamphetamine self-administration. Similar patterns of responding were exhibited during access to 0.1mg/kg methamphetamine self-administration (Stefanski et al., 1999). Importantly, neither of these short access (2hr) studies reported an escalation of intake and responding appeared to be stable across days (Munzar et al., 1999; Stefanski et al., 1999).

Patterns of responding were compared between short access (1-hour) and long access (6-hour) sessions of methamphetamine self-administration (0.05mg/kg and 0.2mg/kg) (Kitumara et al., 2006). Under both conditions there was a short loading phase at the beginning of each session that lasted approximately 10 minutes. Under short access conditions the loading phase consisted of a burst of approximately 9 responses within 10 minutes, after which responding dropped to about 2-3 responses every 10 minutes. In contrast, during extended access conditions there was almost double the responding during the first 10 minutes. However, responding during the maintenance phase remained

remarkably stable and similar to short access conditions with 2-3 responses every 10 minutes. This increase in early responding reflected the gradual escalation of intake that occurred across sessions for extended but not limited access conditions. Furthermore, the escalation of intake was dependent on drug dose, such that responding maintained by higher doses did not increase to the same extent as responding maintained by lower doses. This was likely due to high initial responding that occurred during higher dose self-administration. High responding during the loading phase that progressively increased as a function of day under extended access to methamphetamine self-administration has since been replicated several times (Hadamitzky et al., 2011, 2012; Cozannet et al., 2013; D'arcy et al., 2016).

**Current experiment**

The current experiment set out to document and compare temporal patterns of responding produced under extended access self-administration of MDMA and methamphetamine. Specifically, we wanted to assess whether a gradual escalation of intake as a function of day occurs in a similar manner for self-administration of both drugs and what the nature of this escalation is (loading or maintenance phase). Given the previous literature, we expect to see rapid acquisition of methamphetamine self-administration and more gradual acquisition of MDMA self-administration, however, we expect both groups to exhibit an escalation of intake following acquisition. Furthermore, we expect MDMA responding to exhibit a longer loading phase compared to meth, and less responding during the maintenance phase due to differences in pharmacokinetic profiles.

# Method

## Subjects

Male Sprague-Dawley rats (n=53) were bred in the vivarium at the Victoria University of Wellington, New Zealand. They were housed in groups of 3 or 4 until they reached at least 300g, after which they were housed individually in standard hanging plastic laboratory cages. The vivarium was humidity- (55%) and temperature- (20°C) controlled and was maintained on a 12h light/dark cycle (lights on at 0700). Food and water were available *ad libitum*, except during testing. All procedures were approved by the Animal Ethics Committee of Victoria University of Wellington.

## Surgery

Deep anaesthesia was induced using a combination of ketamine (90mg/kg, IP) and xylazine (9mg/kg, IP). A silastic catheter was inserted into the right jugular and the distal end comprised of 22-gauge stainless steel tubing was passed through to an exposed portion of the skull where it was secured using dental acrylic. Immediately after the surgery Heartmann's electrolyte solution (10.0 ml, SC), and the anti-inflammatory analgesic Carprofen (5.0 mg/kg, SC) were administered. Two days of postoperative care were given in which additional carprofen doses were administered. Daily penicillin (250,000 IU/ml) in heparin (30 IU/ml) solution infusions were administered (0.2mL, iv) in order to maintain catheter patency and prevent infection. Self-administration testing began at least 7 days following surgery.

## Drugs

N-methylamphetamine (methamphetamine) hydrochloride and +/-3,4-methylenedioxymethamphetamine hydrochloride (BDG, Porirua, New Zealand) was dissolved into a sterile saline solution (0.9% NaCl) containing 3 IU/ml heparin. Drug doses refer to the weight of the salt.

**Apparatus**

Self-administration testing was conducted in chambers (Medical Associates, ENV-001) enclosed in sound attenuating closets. The self-administration testing room was humidity- (55%) and temperature- (20°C) controlled. Each chamber was equipped with two levers, an active and inactive lever, and a stimulus light above the active lever. Depression of the active lever resulted in an intravenous infusion of methamphetamine, MDMA or the vehicle and the illumination of the stimulus light. Each infusion (0.1 mL) was delivered during a 12 s period (Razel, Model A. 1rpm equipped motor with a 20 mL syringe). Depressions of the inactive lever were recorded but had no programmed consequences. Daily sessions were 8 hr duration.

**Procedure**

*Methamphetamine* s*elf-administration*: The initial sample consisted of 18 rats. On each day prior to testing the rats were weighed and the catheters were infused with penicillin/heparin (0.2 mL). Each 8-hour daily session began at 0900 and started with an experimenter administered infusion (0.1mg/kg) in order to clear the catheter of the penicillin/heparin solution. Thereafter active lever responses resulted in a drug infusion and the corresponding illumination of the stimulus light according to an FR-1 schedule of reinforcement. In order to reduce the likelihood of overdose, there was a 30 second timeout period after each infusion during which active lever responses had no programmed consequences. At the end of each session, catheters were flushed with 0.2 mL of the penicillin-heparin solution and the rats were returned to the home cage.

Self-administration testing continued for 10 consecutive days. The day following the final test session patency of the catheter was confirmed by the observance of an immediate loss of the righting reflex following an infusion sodium pentobarbital (0.15mL IV, 50mg/mL). One rat died during testing, 3 were removed from the study due to a loss of

catheter patency, data from 2 rats were not used due to equipment failure and data from 1 rat was a statistical outlier. For the remaining 11 rats, we applied an acquisition criterion of 85 responses within the 10 day test period. One rat failed to meet this criterion within the 10-day test period. Thus, 10 of the initial 18 rats completed testing.

*MDMA self-administration*: A separate group of rats ($n$ = 27) was trained to self-administer MDMA in exactly the same manner as for methamphetamine except that the dose was initially 1.0 mg/kg/infusion and no timeout period was implemented. Once a total of 85 infusions had been self-administered, the dose of MDMA was reduced to 0.5 mg/kg/infusion, as in our other studies. One rat died during testing, data from one rat had to be deleted because of equipment failure. Of the remaining 25 rats, 8 failed to acquire self-administration within the 10-day test period, and 5 lost catheter patency. Thus, 12 of the initial 27 rats completed testing.

*Vehicle self-administration:* A final group of rats (n=8) was used to determined operant rates of responding in order to provide a criterion for reliable self-administration of the methamphetamine and MDMA groups. For these rats, each lever depression produced an infusion of the 3 IU heparin vehicle and the illumination of the stimulus light.

Day to acquisition of methamphetamine and MDMA self-administration was determined, in part, by using these operant data. The criteria applied required active lever responding maintained by drug infusions to be greater than responding maintained by vehicle infusions, a preference for the active lever, as indicated by at least 2:1 active:inactive lever responses, and consistency of these two criteria, as indicated by at least 3 consecutive days of meeting these two criteria. The first day that these criteria were met was considered the day to acquisition of self-administration. One methamphetamine rat and 6 MDMA rats failed to

meet these criteria within the 10-day test period. Final sample sizes were 10 methamphetamine and 12 MDMA rats.

**Statistics**

Active and inactive lever responses maintained by methamphetamine, MDMA or vehicle were compared using separate 2-way ANOVAs (Lever X Day). Significant interaction effects were followed by post-hoc analyses to determine the days during which active leer responses were greater than inactive lever responses. The day to acquisition of methamphetamine and MDMA self-administration was compared using a t-test. The total amount of self-administered drug, in mg/kg, was determined for each day of self-administration and separate 1-way ANOVAs were conducted on the data prior to and following acquisition of self-administration of each drug. Total self-administered drug per hour on the first test day, on the first day following acquisition and on the last day of self-administration were analysed using separate 2-way ANOVAS (Day X Hour) for the MDMA and methamphetamine data. Significant effects were followed by post-hoc analyses to probe the nature of the effect.

## Results

A smaller proportion of MDMA self-administering rats met the initial criterion of 85 infusions self-administered drug within the 10-day test period. Of the 11 methamphetamine rats that completed testing, only 1 (9.1%) failed to meet this criterion whereas 6 of the 20 (40%) MDMA rats that completed testing failed to meet this same criterion within the 10-day testing period. One methamphetamine rat and 5 MDMA rats failed to meet the additional criteria for acquisition of self-administration based on the vehicle self-administration data.

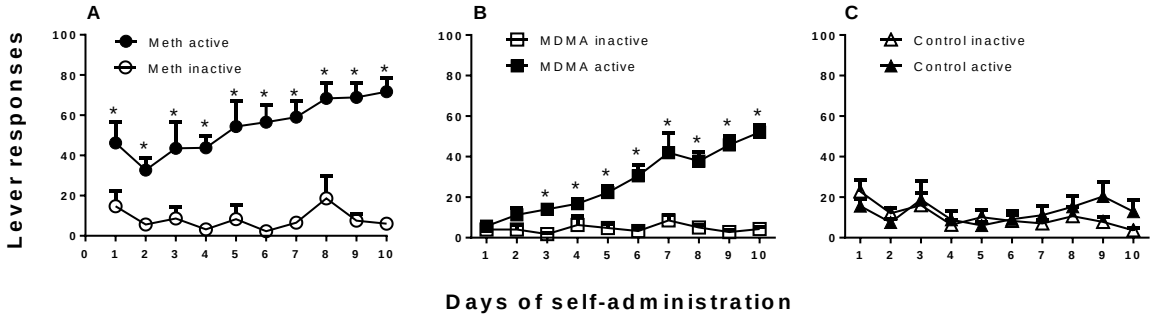


*Figure 1.* Self-administration of methamphetamine, MDMA and vehicle control are displayed. Data points represent average number of responses (+SEM). * indicates significant differences between active and inactive levers $p < 0.05$

Figure 1 shows the number of active and inactive lever responses maintained by methamphetamine (A), MDMA (B) and vehicle (C) self-administration. Self-administration of methamphetamine [$F(9, 81) = 2.38$, $p < 0.019$] and MDMA [$F(9, 99) = 12.05$, $p < 0.001$] progressively increased and a preference for the active lever was produced following the first and third days for the methamphetamine and MDMA groups, respectively. Responding maintained by vehicle infusions remained low and a consistent preference for the active lever was not produced [$F(1, 7) = 0.50$, $p = 0.502$].

While it may look like there is a progressive increase in self-administered drug for both the methamphetamine and MDMA groups, there are two reasons why we are unable to draw such a conclusion from the data presented in Figure 1. First, because the dose of MDMA was reduced to 0.5 mg/kg/infusion once 85 infusions of 1.0 mg/kg/infusion had been self-administered, total active lever responses does not reflect total intake. Figure 2A shows responding maintained by 1.0 mg/kg/infusion MDMA during the last day of self-administration of this dose and by 0.5 mg/kg/infusion MDMA on the first day that this dose was available. There was a significant increase active lever responding between the final day of 1mg/kg/inf MDMA self-administration and the first day of 0.5mg/kg/inf [$t(11) = -3.07$, $p =$

0.011]. Figure 2B shows the mg/kg intake on these 2 test days. There was no significant difference between intake on these 2 days [t (11) = 1.05, $p = 0.32$].

Thus, because the dose of MDMA was decreased on different days for the different rats, responses produced is confounded by drug dose, for this group. We therefore converted responses to mg/kg intake on each day for each rat in both groups.

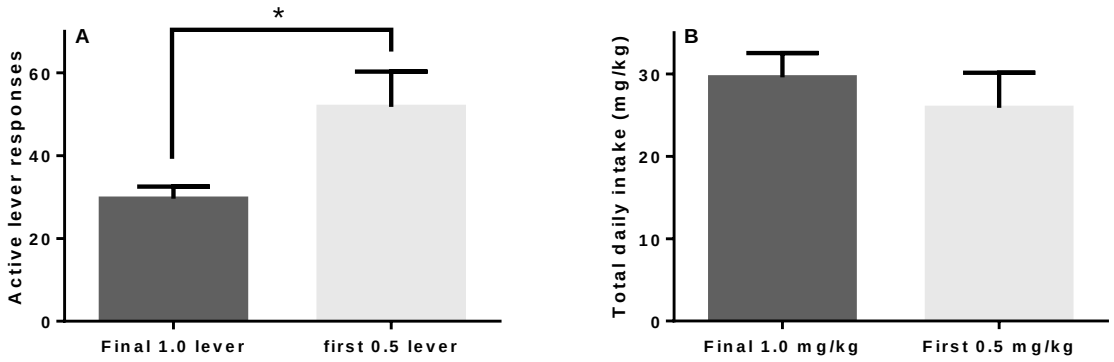


*Figure 2a.* Comparison of active lever responding between last day of 1.0mg/kg MDMA and first day of 0.5mg/kg MDMA (+SEM). * = $p < 0.05$. *Figure 2b* Comparison of mean total daily intake of MDMA (mg/kg) between the final day of 1.0mg/kg MDMA and the first day of 0.5mg/kg MDMA (+SEM).

A second factor that must be considered when interpreting any changes in drug intake as a function of test day is responding during the initial acquisition phase, during which rats are learning the contingency between active lever responses and drug-delivery. Responding during this period can be unreliable and inconsistent. However, following this acquisition period it might be expected that responding becomes more reliable. The latency to acquire reliable self-administration varies between drugs of abuse and an extended latency is typical of MDMA self-administration relative to other psychostimulants such as cocaine (Schenk et al., 2007). Therefore, we implemented an acquisition criterion (see methods) that requires a preference for the active lever, responding above operant rate, and consistency.

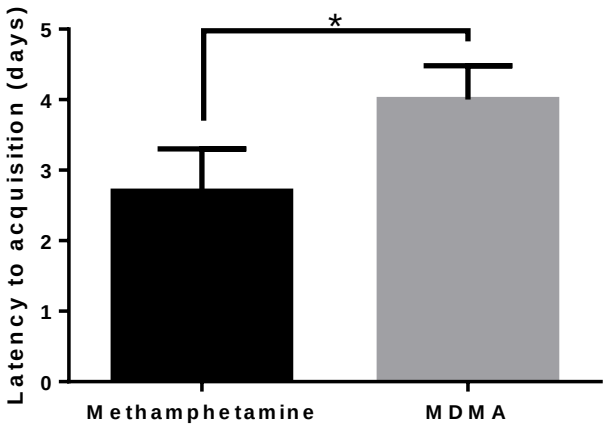


*Figure 3.* comparison of latency to acquire self-administration. Bars represent average latency (+SEM). *= $p < 0.05$

Figure 3 shows the average latency to meet the acquisition criteria. Methamphetamine self-administration was acquired with a shorter latency (range = 1-6 days; mean (SEM) =2.7 days (0.6)) than MDMA self-administration (range = 2-8 days; mean (SEM) = 4 days (0.48) [t (21) = -2.10, $p = 0.048$].

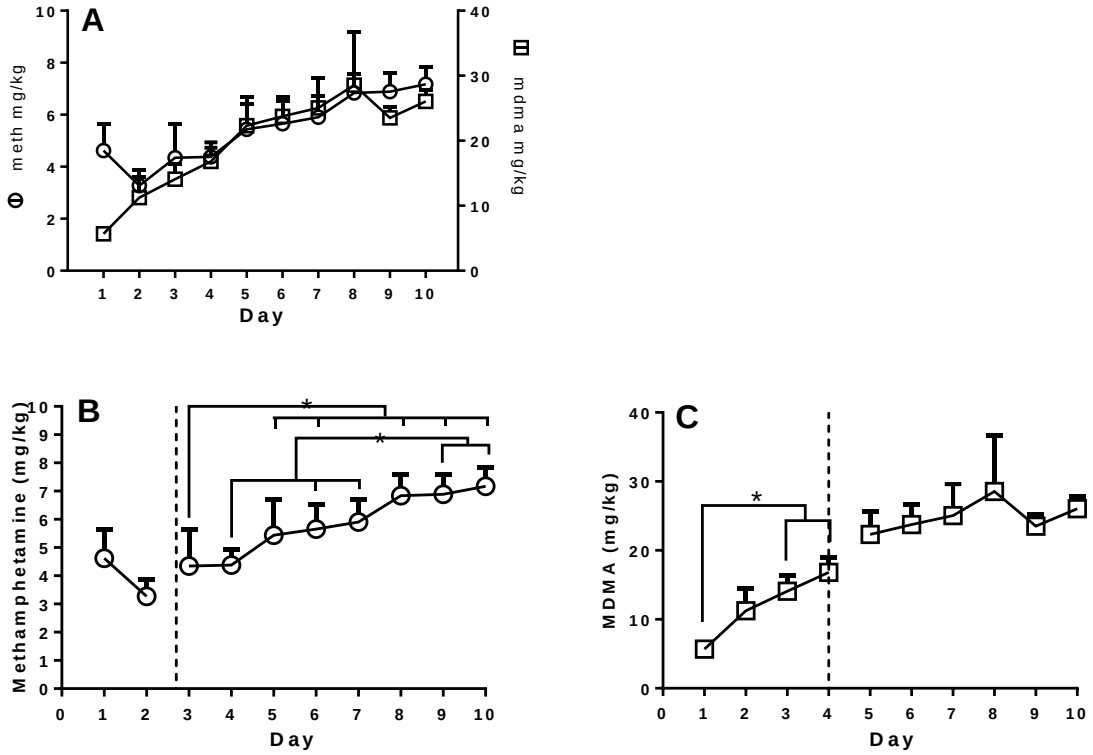


*Figure 4a.* Self-administration of methamphetamine (left axis) and MDMA (right axis) in mg/kg over 10 days of self-administration. Data points represent mean intake (+SEM). 4B. Self-administration of methamphetamine (mg/kg) (+SEM) as a function of day. The vertical dashed line represents the average latency to acquire (2.7) self=administration, data points to the left represent acquisition while data points to the right represent post-acquisition. 4C. Self-administration of MDMA (mg/kg) (+SEM) as a function of day. The vertical dashed line represents the average latency to acquire self-administration (4), data points to the left represent acquisition while data points to the right represent post-acquisition. * = $p < 0.05$

Figure 4 shows the amount of self-administered drug in mg/kg as a function of day. The data in Panel A show both methamphetamine (left axis) and MDMA (right axis) intake across test sessions. These data suggest a remarkable consistency in the pattern of self-administration for both methamphetamine and MDMA. There was a main effect of drug [$F(1, 9) = 44.83$, $p < 0.001$] confirming that more MDMA was self-administered than methamphetamine. Most importantly, intake increased progressively as a function of Day for both methamphetamine and MDMA [$F(9, 90) = 4.06$, $p < 0.001$; $F(9, 90) = 7.69$, $p < 0.001$] self-administration. The vertical line in panels B and C represents the transition from

acquisition to maintenance as derived from the day to acquisition analysis (Day 2.7 for methamphetamine (panel B) and Day 4.0 for MDMA (panel C)). When the acquisition data are taken into account differences in the pattern of self-administration become apparent. Methamphetamine self-administration was rapidly acquired and ANOVA failed to reveal a significant effect of Day during the initial 2-day acquisition period [$F(1, 10) = 0.95$, $p = 0.35$]. During the 8-day post-acquisition phase intake gradually increased [$F(7, 70) = 3.68$, $p = 0.002$] and simple contrasts revealed this effect to be linear [$F(1, 9) = 16.64$, $p = 0.002$, $eta^2 = 0.63$]. Pairwise comparisons were used to probe significant differences between days and showed intake during first day of post-acquisition (day 3) was significantly lower than days 5 [$p = 0.013$], 6 [$p = 0.045$], 8 [$p = 0.046$], 9 [$p = 0.011$], and 10 [$p = 0.011$]. In contrast, acquisition of MDMA self-administration was delayed relative to methamphetamine self-administration and responding during the 4-day acquisition phase gradually increased [$F(3, 33) = 4.62$, $p = 0.008$]. Simple contrasts confirmed this effect to be linear [$F(1, 110 = 9.84$, $p = 0.009$, $eta^2 = 0.47$] and pairwise comparisons showed intake during day 1 was significantly lower than days 3 [$p = 0.012$], and 4 [$p = 0.003$]. In comparison, intake during the 6-day post-acquisition phase remained fairly consistent [$F(5, 50) = 0.45$, $p = 0.81$].

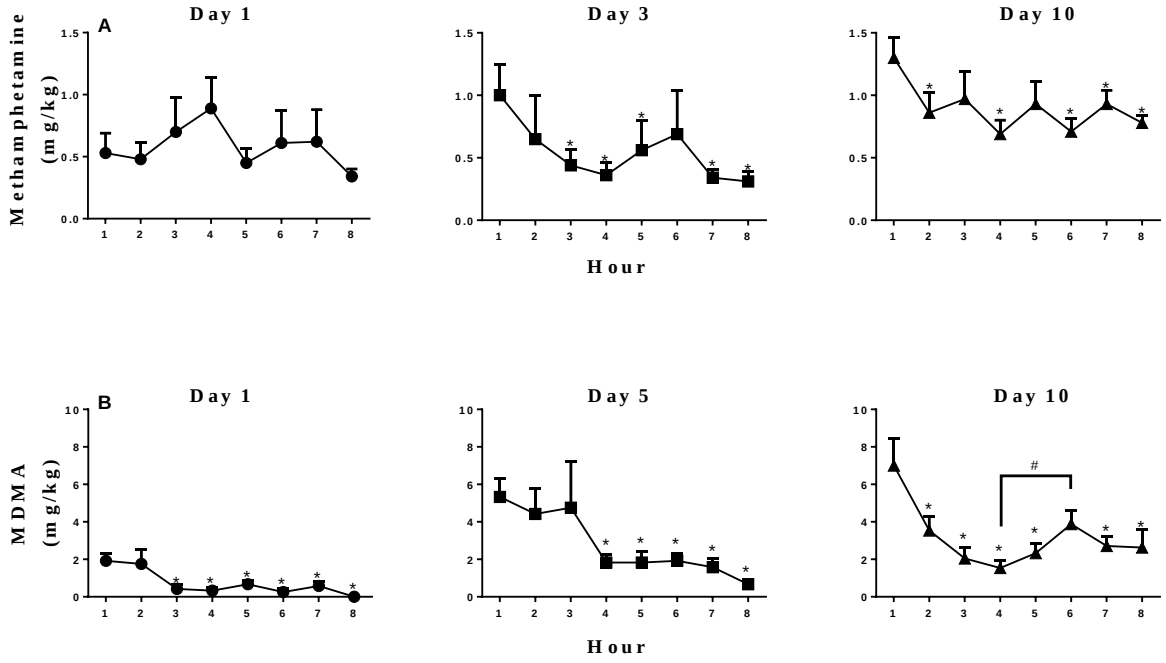


*Figure 5a.* Hourly intake (average (+SEM)) for days 1 (left), 3 (middle), and 10 (right) of methamphetamine. *5b*. Hourly intake (average (+SEM)) for days 1 (left), 5 (middle), and 10 (right) of MDMA. * = $p < 0.05$ compared to the first hour of that day. # = $p < 0.05$ on MDMA day 10 between hours 6 and 4.

Figure 5 shows the intake as a function of hour on Days 1 of testing and for two time periods following acquisition; the first day following acquisition (Day 3 for the methamphetamine rats and Day 5 for the MDMA rats) and Day 10 for both groups.

Panel A shows the pattern of hourly methamphetamine intake for days 1, 3, and 10. During the first day of methamphetamine self-administration there was no effect of hour on drug reinforced responding [$F(7, 70) = 0.88$, $p = 0.53$]. However, on the third day a significant effect of hour was revealed [$F(7, 70) = 2.68$, $p = 0.016$] and was linear in nature [$F(1, 10) = 9.08$, $p = 0.013$, $eta^2 = 0.48$] and pairwise comparisons showed the greatest magnitude of responding occurred within the first hour of the session which was significantly different from hours 3 [$p = 0.007$], 4 [$p = 0.008$], 5 [$p = 0.022$], 7 [$p = 0.004$], and 8 [$p = 0.007$]. Data from the final day of methamphetamine self-administration also revealed a significant effect of hour [$F(7, 70) = 3.16$, $p = 0.006$], however this effect was quadratic in

nature [$F(1, 10) = 14.09$, $p = 0.004$, $eta^2 = 0.59$] suggesting that intake decreased before starting to increase later in the session, however, pairwise comparisons showed that first hour intake was significantly higher than hours 2 [$p = 0.003$], 4 [$p < 0.001$], 6 [$p = 0.005$], 7 [$p = 0.008$], and 8 [$p = 0.002$], but failed to reveal a significant late resurgence of intake as all other comparisons were non-significant.

Panel B shows the pattern of hourly MDMA intake for days 1, 5, and 10 of self-administration. In comparison to methamphetamine, during the first day of MDMA self-administration there was a significant effect of hour [$F(7, 77) = 4.17$, $p = 0.001$]. This effect was linear in nature [$F(1, 11) = 15.37$, $p = 0.002$, $eta^2 = 0.58$] with intake being the highest during the first hour, and lowest during the final hour. However, it is important to note that total MDMA intake during the first day was extremely low (5.67 total responses) as was total intake (5.67mg/kg). On Day 5 of MDMA self-administration, intake had increased and there was a significant effect of hour [$F(7, 77) = 2.45$, $p = 0.025$].The pattern of responding was linear in nature [$F(1, 11) = 15.37$, $p = 0.002$, $eta^2 = 0.58$]. Pairwise comparisons showed intake was greatest during the first hour which was significantly higher thank hours 4 [$p = 0.003$], 5 [$p = 0.003$], 6 [$p = 0.014$], 7 [$p = 0.001$], and 8 [$p = 0.001$]. During the final day of MDMA self-administration, the effect of hour persisted [$F(7, 77) = 4.23$, $p = 0.001$], however rather than the effect following a linear pattern as with earlier days, within-subjects contrasts revealed the pattern of consumption was cubic in nature [$F(1, 11) = 11.48$, $p = 0.006$, $eta^2 = 0.51$]. This suggests intake decreases and increases in a cyclic nature. The cubic pattern of responding can be observed on panel B (right) with intake decreasing past the first hour but later shows a small increase at hour 6 before decreasing again. Furthermore, pairwise comparisons revealed the first hour intake was significantly different from hours 2 [$p = 0.018$], 3 [$p = 0.005$], 4 [$p = 0.003$], 5 [$p = 0.007$], 7 [$p = 0.026$], and 8 [$p = 0.05$], and hour 6 was significantly higher than hour 4 [$p = 0.03$].

## Discussion

The present study set out to document and compare patterns of responding maintained by methamphetamine and MDMA under extended access conditions. It has been suggested that extended access to self-administration produces a behavioural profile characteristic of those with an SUD (Ahmed and Koob, 1998; Ahmed, 2012; Koob and Le Moal, 1997), including a progressive increase in drug intake (escalation of intake) across days of testing (Ahmed and Koob, 1998). Further, responding during extended access sessions is characterised by a relatively short loading phase followed by a longer maintenance phase (Ettenberg et al., 1982; Wilson et al., 1971). Responding within the loading phase has been described as a quick succession of responses which serve the purpose to rapidly elevate blood levels and subsequently produce an efflux of DA in the mesolimbic system (Tsibulsky and Norman, 1999). This is followed by the maintenance phase during which responding becomes regularly spaced in order to maintain blood levels of the drug at the hedonic setpoint (Wise et al., 1995).

The duration of the loading phase and the inter-response intervals during the maintenance phase are directly related to the pharmacokinetic (Tsibulsky and Norman, 1999; Wise et al., 1995), and pharmacodynamic profiles. Self-administration of drugs with a longer half-life would be expected to be characterised by longer inter-response intervals. Also, drugs that preferentially increase dopamine would be expected to be reliably self-administered (Howell and Byrd, 1991; Nader and Mach, 1996; Self et al., 1996; Self and Stein, 1992; Weed and Woolverton, 1995; Yokel and Wise, 1978), whereas those that preferentially stimulate the release of 5HT transmission would not be expected to be self-administered (Rothman and Baumann, 2006; Ritz and Kuhar, 1989; Gerak et al., 2016; Cunningham et al., 2011; Howell and Byrd, 1995; Miszkiel et al., 2012; Munzar et al., 1999; Carrol et al., 1990). Therefore, we selected two amphetamine analogues that differed in both pharmacokinetics

and pharmacodynamics profiles. Methamphetamine has a shorter half-life than MDMA and preferentially stimulates release of DA (Baumann et al., 2002) whereas MDMA preferentially stimulates release of 5HT (Green et al., 1995; 2003). Patterns of responding maintained by self-administration of each drug were then measured during and after an acquisition period. Based on the previous literature, we expected methamphetamine self-administration to be rapidly acquired and a more gradual acquisition of MDMA self-administration due to differences in pharmacodynamic profiles. We expected differences in the temporal pattern of responding maintained by MDMA and methamphetamine infusions due to differences both pharmacokinetic and pharmacodynamic profiles.

**Self-administration acquisition rates and latencies.**

Previous studies have shown methamphetamine self-administration was acquired rapidly under both short (Pickens et al., 1967) and long (Krasnova et al., 2010) access conditions. Acquisition of MDMA self-administration, however, has been described as protracted (Schenk, 2011). In this thesis, methamphetamine self-administration was rapidly acquired (mean = 2.7 days) and in comparison, acquisition of MDMA self-administration was protracted (mean = 4 days). The proportion of rats that acquire self-administration has also been shown to vary as a function of drug. Most rats readily acquired methamphetamine self-administration (Anker et al., 2012; Hadamitzky et al., 2011; Hadamitzky et al., 2012; Kitamura et al., 2006), but a sizable proportion of rats (25%, Highgate and Schenk, 2018; 40%, Schenk et al., 2007; 40%, Schenk et al., 2008; 40% Colussi-Mas et al., 2010; 50%, Schenk et al., 2011; Schenk et al., 2012; Schenk et al., 2016) failed to acquire MDMA self-administration.

Similar results were produced in this study. Almost all rats (90.1%) acquired methamphetamine self-administration, whereas only 60% of the MDMA group acquired self-administration. These data suggest that MDMA is initially a less potent reinforcer than methamphetamine for a large percentage of rats. This might reflect the substantial 5HTergic effects of MDMA. With repeated exposure to MDMA, however, selective deficits in 5HT markers are produced (Cowan, 2007; Kish et al., 2010a, 2010b; McCann et al., 2008; Reneman et al., 2006; Erritizoe et al., 2011; Benningfield and Cowan, 2013; Battaglia et al., 1991; Mamounas et al., 1991; O'Hearn et al., 1988; Scanzello et al., 1992), and subsequently the magnitude of MDMA elicited 5HT decreases (Bradbury et al., 2013). Because 5HT release generally attenuates DAergic activity, deficits in 5HT may enhance the DAergic effects and subsequently facilitate self-administration (Schenk, 2011). This could explain why the latency to acquire MDMA self-administration is prolonged in comparison to methamphetamine, as 5HT deficits may be required for high levels of MDMA self-administration.

Previous experiments have supported the role of 5HT deficits in MDMA self-administration. MDMA induced 5HT efflux was higher in rats that failed to acquire MDMA self-administration compared to rats that met acquisition criteria (Bradbury et al., 2014). Similarly, destruction of 5HT terminals via 5,7 DHT lesions (Bradbury et al., 2014) and genetic deletion of SERT (Oakly et al., 2014) both facilitated MDMA self-administration. Furthermore, deficits in 5HT including MDMA-induced synaptic 5HT (Reveron et al., 2010), 5HT tissue levels (Do and Schenk., 2013), and SERT binding (Schenk et al., 2007) have been demonstrated following MDMA self-administration.

This might also explain why some rats failed to self-administer MDMA to criterion. Rats that did not exhibit sufficient MDMA reinforced responding during early sessions or were less sensitive to the 5HT depleting effects of repeated MDMA might be less prone to

develop high rates of MDMA self-administration. If more extensive testing had been carried out, it is possible a larger proportion of the MDMA self-administering rats could have met acquisition criteria through increased MDMA exposure and the associated 5HT deficits.

**Manipulation of MDMA dose.**

It has been well established that laboratory animals compensate for changes in drug dose by adjusting the rate of responding during self-administration (Panlilio et al., 2003; Panlilio et al., 2007, Wise et al., 1995). In the present study, MDMA self-administration was initiated using a dose of 1.0mg/kg/inf. Once a total intake of 85mg/kg was achieved, the dose was halved (0.5mg/kg/inf) during all remaining sessions. As expected, responding almost doubled during the first day of 0.5mg/kg MDMA self-administration as compared to the final day of 1.0mg/kg/inf MDMA self-administration. This supports the previous literature which has demonstrated a similar change in response rates following the same change in MDMA dose (Schenk et al., 2003; Reveron et al., 2010).

**Acquisition period.**

The acquisition period consists of the first two days of methamphetamine self-administration and the first 4 days for MDMA self-administration. There were no significant differences in methamphetamine intake during the first two days, and responding was relatively high. We speculate methamphetamine intake was high from day 1 due to the drug's potent ability to stimulate synaptic DA and act as a powerful unconditioned reinforcer (Baumann et al., 2002). In comparison, MDMA intake was initially very low with an average of 5.67 mg/kg infused, but significantly increased during this acquisition period. We suggest 5HTergic mechanisms contributed to these low initial response rates. Approximately 80% of

5HT is released following an acute dose of MDMA (Green et al., 2003) following which depletion of 5HT (Finnegan et al., 1988; Gurtman et al., 2002; Kish et al., 2000) as well as a reduction in SERT binding has been reported (Schenk et al., 2007). Therefore, subsequent doses of MDMA may not release 5HT to the same extent of the initial dose due to depleted 5HT and internalization of SERT. Following initial exposure, the DAergic effects of MDMA would be less prone to 5HT inhibition, consequently increasing the potency of MDMA as a reinforcer. This, in turn, would shift the dose effect curve in a predictable manner and increase the response rate maintained by MDMA.

**Post-acquisition period.**

For the methamphetamine group, the post-acquisition period spanned the final 8 days of self-administration testing, during which methamphetamine intake gradually increased as a function of day. This implies an escalation of intake occurred which is a key component of an SUD in humans (Ahmed, 2012). This adds support for the ability of extended access conditions being able to produce such an effect and is consistent with the previous literature regarding extended access methamphetamine self-administration (Ahmed, 2005; Kitamura et al., 2006; Hadamitzky et al., 2011, 2012).

For the MDMA group, the post-acquisition period spanned the final 6 days of testing during which drug intake remained stable and did not significantly increase as a function of day. A failure to observe an escalation of intake for this group was surprising as previous reports of extended access (6-hour) produced an escalation of intake (Highgate and Schenk, 2018; van de Wetering and Schenk, 2019). In those studies, however, MDMA was self-administered during at least 20 daily sessions, compared to 6 sessions in the present study.

With further testing an escalation of MDMA intake during the post-acquisition phase may have been observed.

Unlike the current study however, Ball et al. (2014) reported an escalation of MDMA intake occurred across 10 consecutive 2-hour (short access) sessions in a subgroup of rats based on their behavioural sensitization response to MDMA. Rats that became tolerant to MDMAs locomotor activating effects showed an escalation of MDMA intake, whereas rats that showed locomotor sensitization exhibited stable responding across sessions. However, others have suggested that behavioural sensitization following repeated experimenter administered MDMA can facilitate the acquisition of MDMA self-administration (van de Wetering and Schenk, 2017), as is the case for other psychostimulants (Horger et al., 1990; Piazza et al., 1990; Vezina, 2004). Acquisition of MDMA self-administration is thought to be both $D_1$ and $D_2$ mediated (Brennan et al., 2009), whereas behavioural sensitisation is thought to be $D_2$ but not $D_1$ mediated (Ball et al., 2003; Ramos et al., 2004). Therefore, it may be possible that acquisition of MDMA self-administration and escalation of MDMA intake may be mediated via different DAergic mechanisms. It would have been interesting to measure behavioural sensitization in the current experiment, as it is possible a priori characterisation of behavioural sensitization or tolerance may have revealed group differences in escalation of intake, as well as latency to acquire self-administration.

**Temporal patterns of responding.**

The pattern of responding/intake changed across test sessions. For the methamphetamine group, no significant differences in hourly intake were observed on the first day of self-administration. However, by the first day of post-acquisition testing evidence of a loading phase became apparent, as indicated by high first hour responding, which not

only persisted until the final day of testing but also appeared to increase. Responding during subsequent hours also appeared to increase by the final day, however these were still significantly lower than responding during the first hour.

Munzar et al. (1999) reported that under short access conditions responding progressively decreased within-session during the maintenance phase of methamphetamine self-administration. However, in the current study during the final day of testing, intake during hours 2-8 remained stable and did not decrease as a function of hour like that previously reported under short access conditions. Importantly, no escalation of methamphetamine intake was found under short access conditions (Munzar et al., 1999). Therefore, it is possible for methamphetamine self-administration that an escalation of intake may manifest not only in increased loading phase responding, but also during the subsequent maintenance phase. This contrasts previous findings (Kitamura et al., 2006) that showed methamphetamine intake during the loading phase, but not maintenance phase escalated during extended access. However, self-administration of other stimulants such as cocaine increased during maintenance responding following extended access, albeit not to the same extent as the progressive increase in responding during the first hour (Ahmed, 1998).

On the first day of MDMA self-administration responding was low and therefore the temporal pattern of responding cannot be properly assessed. However, by the first day of post-acquisition testing (day 5) the first hour intake was higher than hours 4-8 but not 2-3. This could suggest the presence of a loading phase that was long in duration, however the large variability seen on this day for hours 2 and 3 suggest that some rats may have exhibited a shorter loading phase than others. Interestingly, responding during hours 4-8 remained low and stable with low variability.

A clearer pattern became apparent by the final day of testing. First hour responding was high (approximately double that of the second hour), and intake progressively decreased during the maintenance phase until hour 6 which exhibited a significant increase from the fourth hour. This might suggest as a strong loading phase that occurs within the first hour, followed by a maintenance phase during which responding progressively decreased until the 4$^{th}$ hour. The increase in responding on the 6$^{th}$ hour may be due to the long elimination half-life MDMA, that is by the 6$^{th}$ hour blood levels of MDMA may fall below the set-point threshold and thus a small increase in responding is exhibited in order to compensate. However, this does still appear to be unusual, as consistent maintenance responding would work to keep MDMA blood levels at setpoint. Alternatively, this could be due to an overshoot of MDMA blood levels produced by high early responding. If that was the case, then with further testing rats may learn to better maintain setpoint and not overshoot, and responding during subsequent hours would become more stable. In support of this, rats with extensive MDMA self-administration experience showed very consistent maintenance responding (Highgate and Schenk, 2018). Regardless, because escalation of MDMA self-administration primarily occurs during the first hour, acute within-session tolerance would not be expected to be responsible (Ahmed, 1998). Therefore, the first hour escalation observed is likely due to between-session tolerance or neuroadaptation that would occur from a high allostatic load from the previous sessions.

Relative to the first hour, responding maintained by methamphetamine during subsequent hours appeared to be greater than that exhibited by MDMA. This is likely due to differences in elimination half-life between these two drugs. In rats, relative to MDMA (Bradbury et al., 2014; Fonsart et al., 2009), methamphetamine has a quick elimination half-life (Melega et al., 1995; Rivière et al., 1999) and therefore would require more frequent responding during the maintenance phase in order to maintain set-point. Furthermore, blood

levels of a drug correlate to DA overflow, both of which are proposed to act as occasion setters for drug reinforcement. Therefore, the rapid elimination of methamphetamine would result in a more frequent availability of reinforcement compared to MDMA.

The current experiment supports the use of extended access self-administration as it can produce behaviours that are similar to those exhibited by those with an SUD such as an escalation of intake. However, the current study has one notable methodological difference from most extended access experiments, which is the lack of 1-hour training sessions and short access controls. Most papers investigating an escalation of drug intake begin by training the animals to self-administer the drug during 1-hour (FR1) self-administration sessions and only when responding is stable do the experimenters split the sample into two groups; one group continues short access self-administration, while the other group is subject to extended access conditions (Kitamura et al., 2006; Larson et al., 2007, Le Cozannet et al., 2013; Ahmed, 2011, 2012; Ahmed and Koob, 1998, 1999; D'Arcy et al., 2016; Edwards and Koob, 2013; Hadamitzky et al., 2012). This not only allows for the comparison of the duration of self-administration sessions, but it also ensures the extended access rats are aware of the lever-drug contingencies from the first day of extended access self-administration testing. Due to a limited number of operant chambers and time constraints, the present study took a different approach and provided rats with extended access self-administration from day 1, therefore not only maintenance, but also acquisition of self-administration took place under extended access conditions. Because of this, we likely observed a more rapid acquisition of self-administration due to increased drug exposure, however, this is speculative as we had no short access conditions to compare to.

## Conclusions

This thesis set out to assess self-administration of two psychostimulants with different pharmacological profiles. As expected, rats acquired methamphetamine self-administration more rapidly than MDMA self-administration. Moreover, a greater percentage of rats acquired methamphetamine self-administration. These findings show the importance of the pharmacological profiles during acquisition.

Differences were also revealed upon analysis of the temporal pattern of responding during different periods of self-administration. These between session changes in response patterns likely resulted from neuroplastic adaptations produced by repeated/prolonged drug exposure. In the case of methamphetamine, we suggest neuroplastic adaptations contributed to the gradual increase of intake, and for MDMA, we suggest the neuroplastic adaptations likely facilitated the acquisition of self-administration.

While our findings are largely in support of the previous literature, it would be of interest to repeat a similar study in the future with several methodological changes to rule out alternative possibilities.

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