

A comparison of repeated MDMA- and AMPH-
produced centre and periphery activity and the
underlying neuroadaptations.

Sarah J. Bradbury

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The recreational use of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') is increasing in New Zealand. MDMA is a ring-substituted derivative of AMPH and, similar to AMPH, produces hyperactivity upon administration. However, the behavioural profile of hyperlocomotion produced by MDMA differs from that produced by AMPH, suggesting that different neural mechanisms underlie the behavioural response. The repeated administration of both MDMA and AMPH induces sensitised hyperactive responses that have recently been found to be different. In the present study, MDMA- and AMPH-induced centre and periphery hyperactivity were compared to investigate the neuroadaptations produced by repeated exposure to the two drugs. Rats were pre-treated with saline, MDMA, or AMPH and the acute response to MDMA, AMPH, or the D₁ agonist, SKF-81297 was measured to determine whether cross-sensitisation was produced. Repeated administration of MDMA and AMPH produced similar behavioural profiles. However, cross-sensitisation between the two drugs was uni-directional, suggesting that the two produce different neuroadaptations. Repeated AMPH, but not MDMA, produced a sensitised response to the hyperlocomotor effects of SKF-81297, suggesting that D₁ receptor mechanisms are one example of different neuroadaptations.

This work is dedicated to my family; dad, mum, and Richie.

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Introduction

(±)-1-phenylpropan-2-amine (amphetamine; AMPH) is a psychostimulant initially synthesised in 1887. The first record of the stimulant effects described AMPH as a compound showing 'pressor' effects (Alles, 1933). In the early 1930s, AMPH was sold by the pharmaceutical company Smith, Kline, and French, as a decongestant to be inhaled (Rasmussen, 2006). In 1936, AMPH was used for the treatment of narcolepsy and a prescription was not required. An estimated 50 million tablets were sold during the first 3 years that it was available (Sulzer, Sonders, Poulsen, & Galli, 2005). A prescription for AMPH was required at the start of 1939, and its use was recommended for a number of medical disorders. Currently, it is prescribed for weight control, narcolepsy, and attention deficit disorder. AMPH and a number of amphetamine-type stimulants are popular amongst young people who use and abuse these substances. Among these stimulants, 3,4-methylenedioxymethamphetamine (MDMA) use has increased markedly and New Zealanders are amongst the highest consumers.

MDMA is a ring-substituted derivative of AMPH with structural similarities to both stimulants and hallucinogens (Green, Mehan, Elliott, O'Shea, & Colado, 2003). MDMA was first synthesised and patented by the German company Merck Pharmaceutical in their search for haemostatic agents (Freudenmann, Oxler, & Bernschneider-Reif, 2006). Aside from a few studies completed by the U.S army in the 1950s, very little research on the effects of MDMA was conducted. In 1976 MDMA was first introduced in a clinical setting in the West Coast of the U.S to facilitate communication (Shulgin, 1986) and was used in clinical settings until MDMA was 'emergency classified' in 1985 (and then permanently classified in 1986) as an illicit drug due to its increasing recreational use and reports of neurotoxicity (MoH, 2004). Recreational ecstasy use has spread worldwide and in New Zealand, in particular, ecstasy use is increasing. In 2007, 6.2% of New Zealand adults had tried ecstasy in their lifetime, with 2.6% of the adult population having used ecstasy in 2007 (MoH, 2010).

Both AMPH and MDMA are drugs of abuse; AMPH is commonly known by the street names: speed, dex, and adderall. It is most commonly ingested in tablet form, or snorted in powder form, but it is also smoked and injected (MOH, 2004). In 2007, 7.2% of New Zealanders surveyed had tried AMPH and/or methamphetamine, and 2.1% of the population reported using in the last 12 months (MOH, 2010). Of those who had used amphetamines in the past 12 months, 58.2% had consumed amphetamine sulphate (speed; MOH, 2010).

MDMA is usually consumed in tablet form and is sold under many names with ecstasy, E, adam and XTC being the most common (Shulgin, 1986). The content of ecstasy tablets differs greatly; additional to MDMA, other illicit drugs found in NZ tablets are: 3, 4-Methylenedioxyamphetamine (MDA); 3,4-Methylenedioxy-*N*-ethylamphetamine (MDEA); methamphetamine; AMPH; and ketamine (ESR, 2000).

Drug abuse and dependence

Drug abuse and dependence have been differentiated by the pattern of drug-taking. Both abusers and dependents consume large quantities of drug but the intake of drug dependent individuals is compulsive and uncontrolled whereas the intake of abusers is more regular. The DSM IV describes drug abuse as a condition characterised by a maladaptive pattern of drug use that leads to impairments in meeting work or home obligations, and social or interpersonal problems (APA; 2000). Drug dependence is described as a pattern of drug use where the drug is often taken in larger amounts or over a longer period than is intended, and where there is a persistent desire or unsuccessful effort to cut down or control substance use (APA, 2000).

A wealth of data suggests that genetic (Kendler, Karkowski, Neale, & Prescott, 2000; Nestler, 2000), biological (Robinson & Berridge, 1993; Lyvers, 2000; Koob & Le Moal, 2001), and environmental and social factors (e.g Brook, Whiteman, Finch, & Cohen, 2000; Kendler et al., 2000) render some individuals more susceptible to the drug-induced neural adaptations that underlie drug

dependence. These changes include molecular changes that facilitate neuroplastic changes, and the neuroplastic changes themselves (for a review see Kalivas, 2002). The elucidation of these neuroadaptations is important so as to understand the neural underpinnings of drug dependence, including AMPH and MDMA dependence.

AMPH pharmacology

AMPH increases synaptic levels of the neurotransmitters dopamine (DA), norepinephrine, and serotonin (Heikkila, Orlansky, & Cohen, 1975; Axelrod, Whitby, & Hertting, 1961; Curet, De Montigny, & Blier, 1992; Kuczenski, Segal, Cho, & Melega., 1995; Eshleman et al., 1999; Rothman et al., 2001) but the effect on DA neurotransmission has received the greatest attention (Rothman et al., 2001). AMPH releases DA through two sodium-dependent DA transporter (DAT)-mediated mechanisms; stimulation of release, and reuptake blockade (Fischer & Cho, 1979; Raiteri, Cerrito, Cervoni, & Levi, 1979). The uptake inhibiting effects of AMPH may be due to AMPH competing with DA as a substrate for the transporter (Seiden, Sabol, & Ricaurte, 1993). AMPH-induced DA release has been proposed to occur through the *exchange diffusion model* (Fischer & Cho, 1979), whereby an AMPH molecule is transported from the synapse to the inside of the neuron (and blocks DA reuptake in doing so) where it is released. Following the release of AMPH, the model proposes that a DA molecule is transported from the inside of the neuron to the synapse. Debate exists as to whether transporter-mediated AMPH movement into the neuron is the sole facilitator of DA release (Fischer & Cho, 1979), or whether it is the transporter-mediated and passive AMPH diffusion into the neuron that facilitates AMPH-induced DA release (Liang & Rutledge, 1982).

In addition to non-vesicular DA release, AMPH stimulates the release of DA from vesicles into the cytoplasm (Parker & Cubeddu, 1986; 1988) and prevents the movement of cytoplasmic DA into vesicles (Philippu & Beyer, 1973). This occurs through the alkalinisation of vesicles (Seiden et al., 1993). Moreover, high doses of AMPH further increase DA levels by inhibiting the actions of the DA-

degrading enzyme, monoamine oxidase (MAO; Mantle, Tipton, & Garrett, 1976; Clarke, Miller & Shore, 1979).

MDMA pharmacology

The predominant neurochemical effects of MDMA are on the serotonin (5-HT) system. Acute administration of MDMA in rats produced a rapid release of serotonin as evidenced by a decrease in tissue 5-HT levels in the hours following MDMA administration (Colado & Green, 1994; Commins et al. 1986), and increased levels of synaptic 5-HT as measured by *in vivo* microdialysis (Gough, Ali, Slikker & Holson 1991; Yamamoto, Nash, & Gudelsky, 1995; Gudelsky & Nash, 1996; Sabol & Seiden, 1998; Shankaran & Gudelsky, 1999; Nixdorf, Burrows, Gudelsky, & Yamamoto, 2001; Mechan et al., 2002a). Release of 5-HT is produced as a result of MDMA binding to, and reversing, the 5-HT transporter (SERT; Battaglia, Brooks, Kulsakdinun, & De Souza, 1988; Rudnick & Wall, 1992); and by inhibiting 5-HT uptake into terminal vesicles through the binding to vesicular monoamine transporters, thus increasing the cytosolic pool of 5-HT (Brodkin, Malyala, & Nash, 1993) that is then released into the synapse by the reversed SERT.

Like AMPH, MDMA also increases extracellular DA (Sabol & Seidon, 1998; Bankson & Yamamoto, 2004). The mechanism is, however, different because MDMA produces effects on both impulse- and transporter- mediated DA release. The impulse-mediated release appears to be modulated by the 5-HT system (Koch & Galloway, 1997), since MDMA-induced striatal DA release was attenuated following blockade of MDMA-induced 5-HT release (Gudelsky & Nash, 1996; Koch & Galloway, 1997). Support for the idea of DAT-mediated DA release comes from research using fast cyclic voltammetry, where DA release in brain slices following pressure-ejected MDMA was found to be due to interactions with the DA transporter (Iravani, Asari, Patel, Wieczorek, & Kruk, 2000). Further, the DA uptake inhibitors, GBR 12909 or mazindol, blocked MDMA-produced DA release (Nash & Brodtkin, 1991; Koch & Galloway, 1997). However, one study has shown that GBR had no effect on MDMA-produced DA release (Mechan et al., 2002a).

Behavioural effects of AMPH and MDMA

Due to the differences in AMPH and MDMA pharmacology, the behavioural effects of the drugs may also be expected to differ. The effects of drugs on dopaminergic transmission can be inferred by increased locomotor activity of rats. Evidence for a role of DA in locomotion is plentiful; central administration of DA (Pijnenburg, Honig, Van der Heyden, & Van Rossum, 1976), and systemic administration of DA receptor agonists stimulated hyperlocomotion. There are two DA receptor families: the D1-like receptors comprise the D1 and D5 receptors; and the D2-like receptors comprise the D2, D3, and D4 receptors. Acute administration of either a D1 or D2 agonist produced hyperactivity (Mazurski & Beninger, 1991; Salmi, Malmgren, Svensson, & Ahlenius, 1998).

AMPH-produced hyperlocomotion has been attributed to enhanced DA neurotransmission. Both D1-like and D2-like antagonists, administered centrally or systemically, (Bardo, Valone, & Bevins, 1999; Depoortere et al., 2003; Mazurski & Beninger, 1991; Mithani, Martin-Iverson, Phillips, & Fibiger, 1986) blocked AMPH-produced hyperactivity, as did the administration of the selective neurotoxin, 6-OHDA (Kelly, Seviour, & Iverson, 1975; Kelly & Iverson, 1976).

Dopaminergic mechanisms also mediate MDMA-produced hyperactivity. Neurotoxic lesions (Gold, Hubner, & Koob, 1989) and peripherally-administered receptor antagonists reduced or blocked MDMA-induced hyperlocomotion (Kehne et al., 1996; Ball, Budreau, & Rebec, 2003; Bubar, Pack, Frankel, & Cunningham, 2004; Daniela et al., 2004). Of interest, Ball et al. (2003) reported a late-onset of MDMA-induced hyperlocomotion following the D1 antagonist, SCH 23390. These effects have been attributed to the short half-life of SCH-23390.

Although both AMPH and MDMA produce a hyperlocomotor response, the behavioural profile of the locomotion differs between the drugs. MDMA produces thigmotaxis that leads to an avoidance of the central area of an open field (Adams & Geyer, 1985a; Rempel, Callaway & Geyer, 1993; McCreary, Bankson, & Cunningham, 1999; Ludwig, Mihov, & Schwarting, 2008) whereas

AMPH does not lead to an avoidance of the centre to the same extent. The thigmotaxic response found with MDMA was comparable to the behavioural response to hallucinogens (Bankson & Cunningham, 2001).

The differing behavioural response to AMPH and MDMA may be a reflection of the different pharmacology of the two drugs, and further, the profile of the drug-produced hyperlocomotion may provide a means to determine neuroadaptations resulting from the repeated administration of these drugs.

Effects of repeated exposure to AMPH or MDMA

Repeated, intermittent administration of psychostimulants can produce both behavioural and neurochemical sensitisation. This augmented response was first reported in the 1930s (Tatum & Seevers, 1931; Downs & Eddy, 1932) and it has been suggested that this might be a mechanism underlying the development of compulsive drug taking and seeking (Robinson & Berridge, 1993). Indeed, following repeated exposure, rats became sensitised to the positively reinforcing effects of stimulants as indicated by decreased latencies to acquisition of self-administration (Piazza, Deminiere, le Moal, Simon, 1990; Schenk & Partridge, 2000; Suto et al., 2002), and increased motivation to self-administer drugs (Mendrek, Blaha, & Phillips, 1998; Vezina, Pierre, & Lorrain, 1999; Lorrain, Arnold, & Vezina, 2000). Thus, the study of neural processes underlying sensitisation might provide information concerning the neural mechanisms underlying the development of drug abuse.

A simple and reliable method of measuring behavioural sensitisation is to examine changes in drug-produced hyperactivity following repeated drug exposure. A large number of studies has shown that repeated exposure to AMPH resulted in a sensitised response that was reflected in increased peripheral as well as central activity. Thus, the sensitised response reflected an amplification of the acute effects, with more activity in both areas of an open field.

The behavioural profile of the sensitised MDMA response differed from the acute MDMA response and from what has generally been reported following repeated exposure to AMPH. Activity in the centre of an open field was increased to a greater extent than activity in the periphery following repeated MDMA exposure (McCreary et al., 1999; Colussi-Mas & Schenk, 2008). This disparity between the sensitised responses following repeated exposure to the two drugs suggests that different neural adaptations underlie AMPH- and MDMA- induced sensitisation. One way to investigate these neural adaptations is to characterise the neurochemical changes produced by a sensitisation regimen.

DA and sensitisation

Several studies have implicated sensitisation in dopaminergic substrates as a mechanism underlying behavioural sensitisation. For example, sensitised DA release in the nucleus accumbens (Wolf, White, Nassar, Brooderson, & Khansa, 1993; Kalivas, Duffy, & White, 1998; Shim et al., 2001; Ding, Rodd, Engleman, & McBride, 2009; Cope et al., 2010; Desai, Paronis, Martin, Desai, & Bergman, 2010) and medial pre-frontal cortex (Hedou, Homberg, Feldon, & Heidbreder, 2001) was found following pre-exposure that led to a sensitised locomotor response. Further, following longer withdrawal periods both behavioural and dopaminergic responses were elevated to a greater extent than following shorter withdrawal periods (Kalivas & Duffy, 1993; Paulson & Robinson, 1995, Pierce & Kalivas, 1997).

Cross-sensitisation

Augmented DA transmission has been widely studied as a neurochemical underpinning of the expression of AMPH-induced sensitisation and, to a lesser extent, MDMA-induced sensitisation. One method used to investigate this makes use of studies of cross-sensitisation. Cross-sensitisation refers to the phenomenon whereby sensitisation induced by pre-treatment with one drug is expressed following (crosses to) administration of a different drug.

Drugs of abuse cross-sensitise in the self-administration paradigm; rats pre-treated with AMPH showed enhanced cocaine self-administration (Horger, Giles, & Schenk, 1992; Valadez & Schenk, 1994; Fletcher, Robinson, & Slippoy, 2001; Suto et al., 2002); and rats pre-treated with cocaine demonstrated greater motivation to self-administer AMPH (Liu, Morgan, & Roberts, 2007). MDMA pre-treatment also facilitated cocaine self-administration; MDMA pre-treated rats acquired cocaine self-administration more quickly than saline pre-treated rats (Fletcher et al., 2001). Moreover, MDMA amphetamine-seeking was demonstrated following an MDMA prime to rats that had received MDMA pre-treatment (Morley, Cornish, Li, & McGregor, 2004). These findings showed that the positively reinforcing effects of AMPH crossed over with those of MDMA, and both crossed with cocaine, suggesting common neuroadaptations as a result of preexposure.

Cross-sensitisation experiments commonly use a sensitisation drug administration regimen whereby animals sensitised to one drug are then administered a challenge injection of a different drug, and the resulting neurochemical and/or behavioural response is measured. Drug-induced locomotion is an easily-quantified behavioural response. As DA has been implicated in drug-induced hyperactivity, such research has focussed on dopaminergic mechanisms of cross-sensitisation. A locomotor response to the challenge drug, comparable to the response of animals sensitised to that challenge drug, suggests that the pre-treated and challenge drugs share a common neural mechanism to mediate sensitisation.

The cross-sensitisation found in research using self-administration experiments has also been found in studies measuring locomotion. Rats that were pre-treated with AMPH were more responsive to the locomotor activating effects of cocaine (Kalivas & Weber, 1988; Suto et al., 2002). Rats pre-treated with MDMA were also more sensitive to cocaine- (Kalivas et al., 1998) but not to AMPH- or methylphenidate-produced hyperactivity (Modi, Yang, Swann, & Dafny, 2006).

AMPH pre-treated rats were also more sensitive to the locomotor activating effects of nicotine (Santos, Marin, Cruz, DeLucia, & Planeta, 2009) and morphine (Bjijou, Stinus, Le Moal, &

Cador, 1996) but a failure to observe cross sensitisation to morphine has also been observed (Vanderschuren, Schoffemeer, Mulder, & De Vries, 1999). The discrepancies in the results reflect the differences in procedures used by the two groups; Bjijou et al (1996) injected the two drugs directly into the ventral tegmental area (VTA), whereas Vanderschuren et al (1999) administered the drugs peripherally.

The role of D₁-like receptors in the expression of AMPH-induced sensitisation has not been the subject of much research and is therefore undetermined. AMPH pre-treatment failed to sensitise rats to the locomotor activating effects of the D₁ agonist, SKF- 82958, (Vanderschuren, Schoffemeer, Mulder, & De Vries, 1999). The lack of a sensitised response to a D₁ agonist is unexpected given that repeated AMPH produced sensitised DA (Wolf et al., 1993; Kalivas, et al., 1998; Hedou, et al., 2001; Shim et al., 2001; Ding, et al., 2009; Cope et al., 2010; Desai, et al., 2010). However, Vanderschuren et al. (1999) offered that augmented DA release does not function to mediate sensitised behavioural responses, but rather to maintain circuitry responsiveness.

The role of the D₁ receptor in the expression of MDMA-induced sensitisation has been subject to little research. The D₁ antagonist SCH-23390 and the D₁ agonist SKF-81297 blocked the expression of MDMA-induced locomotor sensitisation (Ramos, Goni-Allo, & Aguirre, 2004; 2005). Clearly, additional research is required in order to understand the role of DA receptors in sensitisation to the behavioural effects of MDMA.

Present Research

The present research was undertaken to compare the MDMA- and AMPH-produced neuroadaptations produced by repeated exposure to the drugs. Because of the different profile of MDMA- and AMPH-produced hyperactivity, hyperlocomotion will be measured by using an open-field divided into a central zone and a periphery.

Firstly, in an effort to replicate previous research, the behavioural profiles of acute and repeated MDMA and AMPH were observed. Then, to investigate whether any common neuroadaptations are produced with repeated MDMA and AMPH, the effects of MDMA and AMPH pre-treatment on the acute response to AMPH and MDMA, respectively, will be analysed. Finally, the locomotor activating effects of the D₁ agonist, SKF 81297, will be measured following repeated MDMA and AMPH to contrast and compare the role of D₁ receptor mechanisms.

Method

Animals

Male Sprague-Dawley rats (n=396) were bred in the vivarium at Victoria University of Wellington, New Zealand. The housing rooms were temperature- (21°C) and humidity- (55%) controlled, and water and food were available *ad libitum*. A 12/12 hour light/dark cycle system was imposed with lights on at 7am. Rats were housed in groups of four from weaning until 3 days before testing commenced, at which time the rats were separated and housed individually. All experimental protocols were approved by the Animal Ethics Committee of Victoria University of Wellington.

Apparatus

Sixteen clear, open-field Plexiglas chambers (Med Associates Inc, USA; model ENV-515) measuring 42 x 42 x 30cm set in sound-attenuated boxes were used to measure horizontal locomotion. Four sets of sixteen infra-red sensors spaced evenly along the sides of each box produced a lattice of beams, creating squares of dimension 25mm x 25mm. The sequential

interruption of a group of three beams was the approximate size of the body of the rat and was recorded as one activity count.

The chambers were divided into two areas: the central zone was defined as the central 19 x 19 cm of the open field, and the remaining area was defined as the periphery. A white noise generator was used during the experiments to mask any outside noise. Prior to each test, chambers were wiped with Virkon 'S' disinfectant (Southern Veterinary Supplies, NZ). All experiments were run in the dark between 0700 and 1900 hours.

Methods

During a 5-day pre-treatment phase, rats received daily injections of MDMA (10.0 mg/kg), AMPH (2.0 mg/kg) or the saline vehicle. Locomotor activity was measured on all of these days. Following a 2 day no-drug period, during which the rats remained in the home cage, the locomotor activating effects of a number of drugs was determined. In each of these tests, the rats were placed in the activity boxes and, following a 30 min habituation period the drug injection was administered. Locomotor activity was recorded at 5 min intervals during the 30 min pre-injection and 60 minutes post-injection periods. Table 1 shows the pre-treatment drugs and test drugs that were administered.

Pre-treatment Drug		Challenge Drugs	
MDMA	MDMA	AMPH	SKF-81297
(10.0mg/kg)	0.0mg/kg (n=11)	0.0mg/kg (n=7)	0.0mg/kg (n=15)
	2.5mg/kg (n=12)	0.5mg/kg (n=8)	1.0mg/kg (n=7)
	5.0mg/kg (n=12)	1.0mg/kg (n=8)	2.0mg/kg (n=8)
	10.0mg/kg (n=12)	2.0mg/kg (n=8)	
Saline	MDMA	AMPH	SKF-81297
(0.9%)	0.0mg/kg (n=8)	0.0mg/kg (n=14)	0.0mg/kg (n=14)
	2.5mg/kg (n=11)	0.5mg/kg (n=8)	1.0mg/kg (n=6)
	5.0mg/kg (n=11)	1.0mg/kg (n=6)	2.0mg/kg (n=8)
	10.0mg/kg (n=12)	2.0mg/kg (n=6)	
AMPH	MDMA	AMPH	SKF-81297
(2.0mg/kg)	0.0mg/kg (n=8)	0.0mg/kg (n=14)	0.0mg/kg (n=13)
	2.5mg/kg (n=7)	0.5mg/kg (n=8)	1.0mg/kg (n=9)
	5.0mg/kg (n=8)	1.0mg/kg (n=8)	2.0mg/kg (n=8)
	10.0mg/kg (n=8)	2.0mg/kg (n=8)	

Table 1. Summary of pre-treated and test drugs.

Drugs

MDMA (\pm 3,4-methylenedioxymethamphetamine hydrochloride) was obtained from ESR (Porirua), AMPH (d-amphetamine sulphate) from Sigma Aldrich (NZ Ltd), and SKF-81297 from Tocris (Abacus ALS).

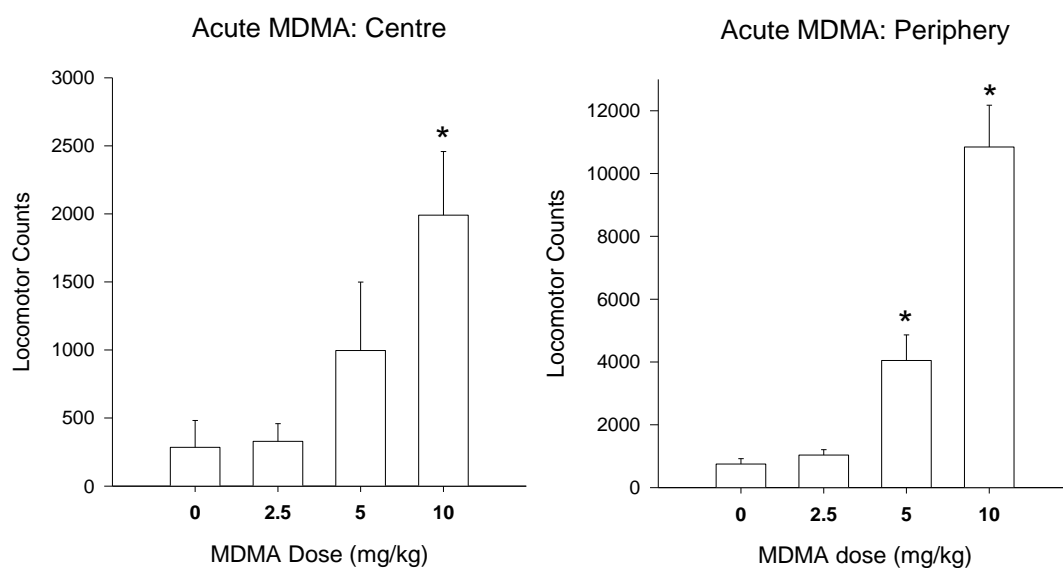
Data Analysis

Locomotor activity counts in the centre and periphery were recorded by Act Monitor and effects of pre-treatments on activity in each region of the open field were analysed using the Statistical Package for the Social Sciences (SPSS, v.16). Separate 1-way ANOVAs first compared locomotor activating effects of MDMA or AMPH as a function of dose in the saline pre-treated rats. Thereafter, separate 2-way ANOVAs (pre-treatment x dose) compared effects of saline and either MDMA or AMPH pre-treatment on activity produced by the various drugs. Subsequent analyses using either 1-way ANOVAs or Tukey post-hoc tests compared activity of saline-pre-treated and MDMA- or AMPH-pre-treated groups.

Results

Part I: Acute effects of MDMA and AMPH

Figure 1 shows total locomotor activity counts, and counts in both the central and peripheral zones (\pm SEM) during the 60 minutes following acute administration of MDMA.



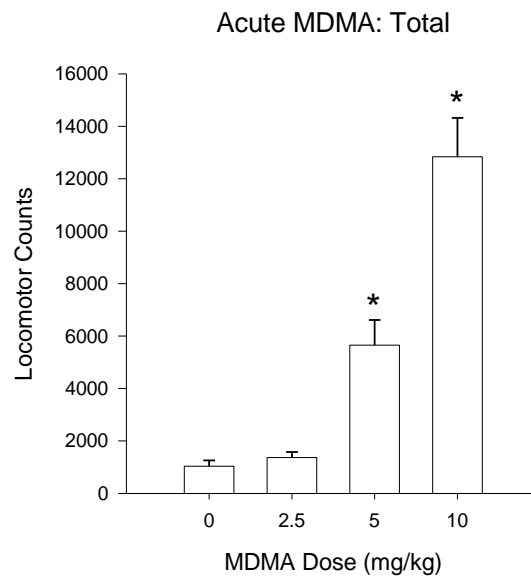


Figure 1. Effect of acute MDMA on locomotor activity. Rats received an injection of MDMA (0.0, 2.5, 5.0, or 10.0 mg/kg). Bars represent the average total locomotor counts produced across the total area, central zone, and periphery (\pm SEM). * $p < 0.05$ vs 0.0mg/kg dose

Acute MDMA produced a significant increase in activity in all areas: open field: $F(3, 39) = 30.829$, $p < 0.0001$; central zone: $F(3, 39) = 10.601$, $p < 0.001$; and peripheral zone: $F(3, 39) = 25.383$, $p < 0.001$). Post-hoc analyses revealed that the 2.5mg/kg dose of MDMA failed to increase activity in any area. The 5.0mg/kg dose failed to significantly increase activity in the central zone, but increased total and peripheral zone activity ($p < 0.05$). The 10.0mg/kg dose significantly increased activity in all three zones ($p < 0.0001$).

Figure 2 shows total locomotor activity counts, and counts in both the central and peripheral zones (\pm SEM) during the 60 minutes following acute administration of AMPH.

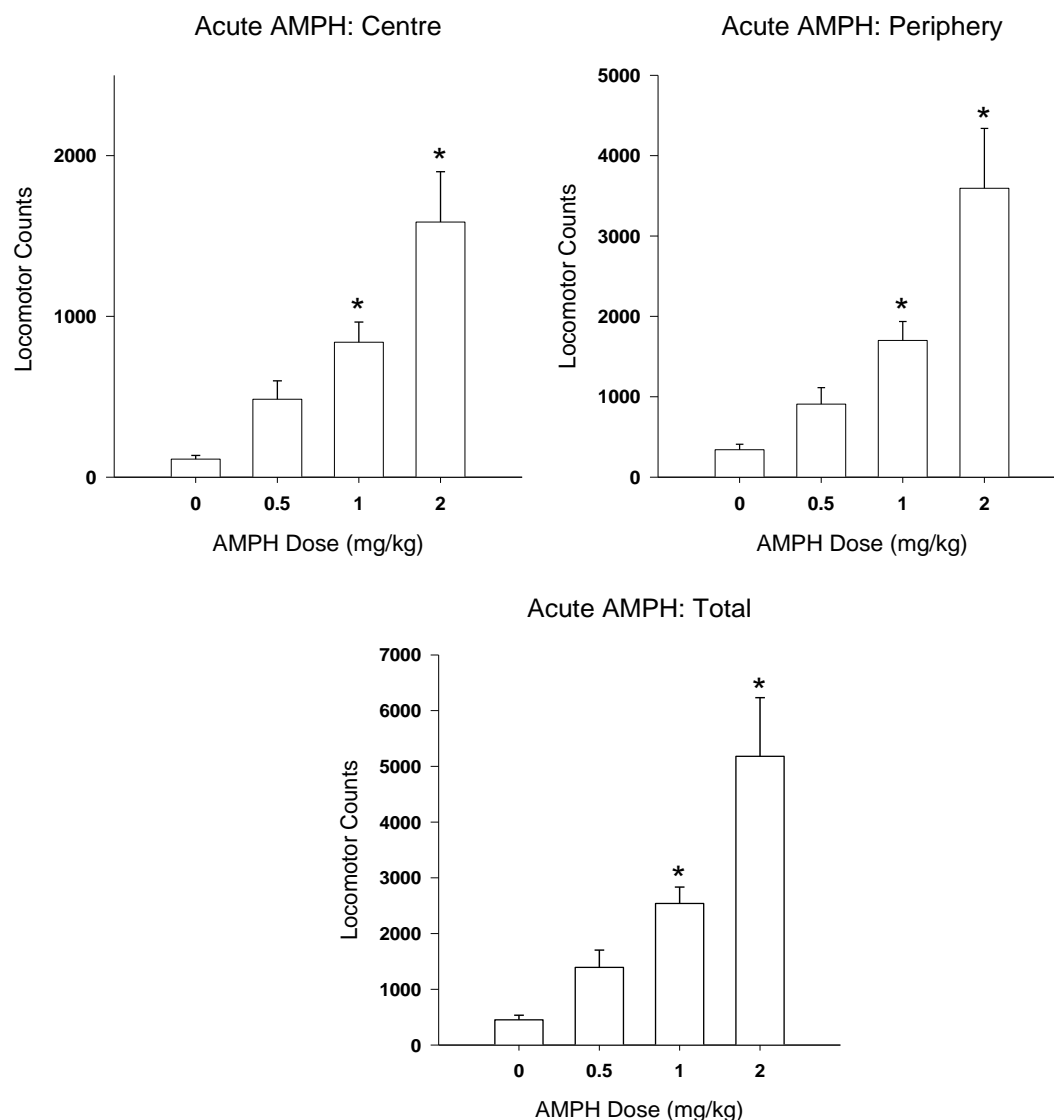


Figure 2. Effect of acute AMPH on locomotor activity. Rats received an injection of AMPH (0.0, 0.5, 1.0, or 2.0 mg/kg). Bars represent the average total locomotor counts 60 minutes following AMPH injection produced across the total area, central zone, and periphery (\pm SEM). * $p < 0.05$ vs 0.0mg/kg dose.

Acute AMPH produced a significant increase in activity across all areas (open field: $F(3, 30) = 23.237$, $p < 0.0001$; central zone: $F(3, 30) = 22.772$, $p < 0.0001$; and peripheral zone: $F(3, 30) = 21.738$, $p < 0.001$). Post- hoc analyses revealed that effects of the 0.5mg/kg dose of AMPH did not significantly differ from effects of the 0mg/kg in any area. The 1.0mg/kg dose produced a significant increase in total, central, and peripheral activity ($p < 0.05$ for each). The 2.0mg/kg dose also significantly increased total ($p < 0.0001$), central ($p < 0.0001$) and peripheral ($p < 0.0001$) activity.

As can be seen in Figures 1 and 2, MDMA-produced activity counts were much greater than activity produced by AMPH. Additionally, it appeared that most of the increase in MDMA activity was due to increased peripheral rather than central activity, and that there might be differences between effects of increasing doses of the two drugs. Previous research (Adams & Geyer, 1985a; Rempel et al., 1993; McCreary et al., 1999; Ludwig et al 2007) has found the behavioural profile of acute MDMA to differ from AMPH, in that MDMA rats display a thigmotaxic response and avoid the centre.

In order to compare the current results with the above literature, AMPH and MDMA central and peripheral activity is graphed in Figure 3 as a percentage of total activity during the 60 minutes following the drug challenge injection on day 8. The two drugs are compared across 4 doses: Dose 0 (MDMA 0.0mg/kg and AMPH 0.0mg/kg), Dose 1 (MDMA 2.5mg/kg and AMPH 0.5mg/kg), Dose 2 (MDMA 5.0mg/kg and AMPH 1.0mg/kg), and Dose 3 (MDMA 10.0mg/kg and AMPH 2.0mg/kg).

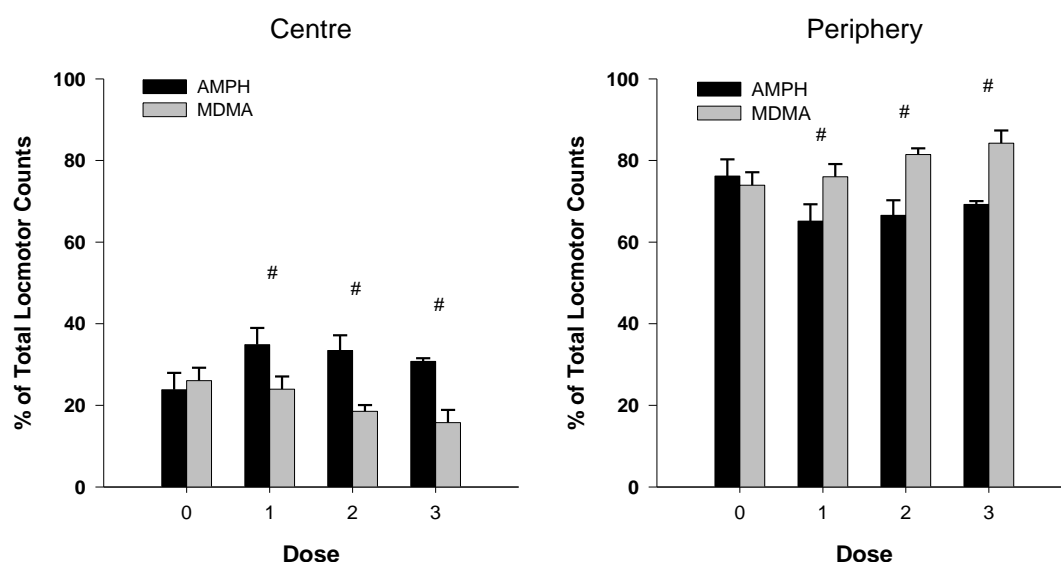
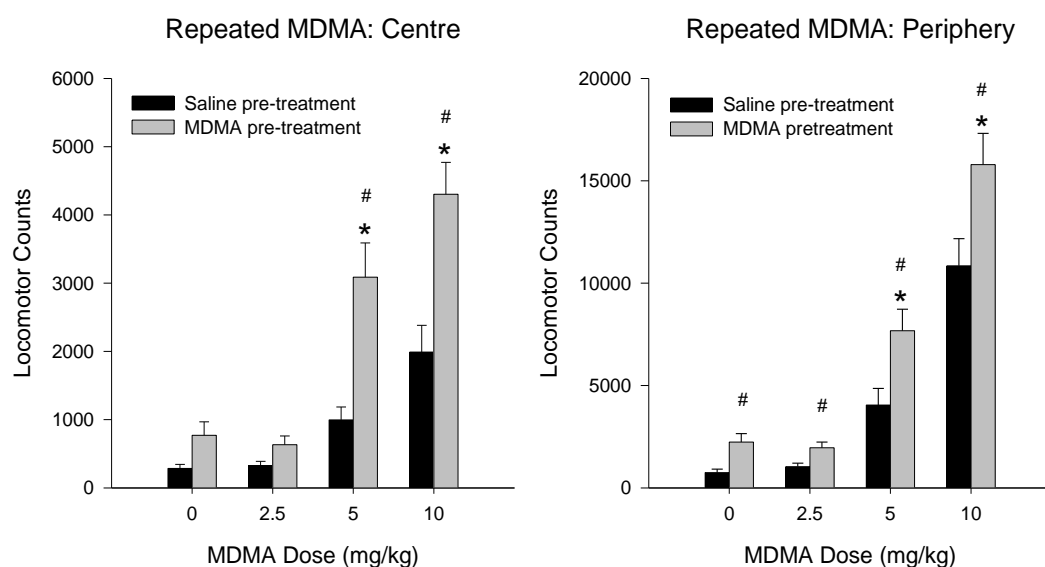


Figure 3. Centre and Peripheral activity as a percentage of total locomotor activity counts for each drug on day 8. Dose 0 = 0.0mg/kg AMPH and 0.0mg/kg MDMA, Dose 2 = 0.5mg/kg AMPH and 2.5mg/kg MDMA, Dose 3 = 1.0mg/kg AMPH and 5.0mg/kg MDMA, and Dose 4 = 2.0mg/kg AMPH and 10.0mg/kg MDMA. # $p < 0.05$ AMPH vs MDMA.

A main effect of Drug ($F(1, 74) = 14.407, p < 0.0001$), and a significant interaction between Drug and Dose ($F(3, 72) = 2.786, p < 0.05$) were found. Post-hoc analyses showed AMPH and MDMA significantly differed at Doses 1 ($p < 0.05$), 2 ($p = 0.01$) and 3 ($p = 0.01$) indicating that animals spend less time in the centre (and more time in the periphery) after MDMA than after AMPH. A trend for MDMA to decrease centre activity (and increase periphery activity) with increasing dose was also found ($p = 0.055$).

Part II: Sensitisation to the effects of MDMA and AMPH

Figure 4 shows the average total, centre, and periphery activity (+ SEM) during the 60 minutes following an injection of MDMA (0.0, 2.5, 5.0, or 10.0mg/kg) on the challenge day of the sensitisation regimen.



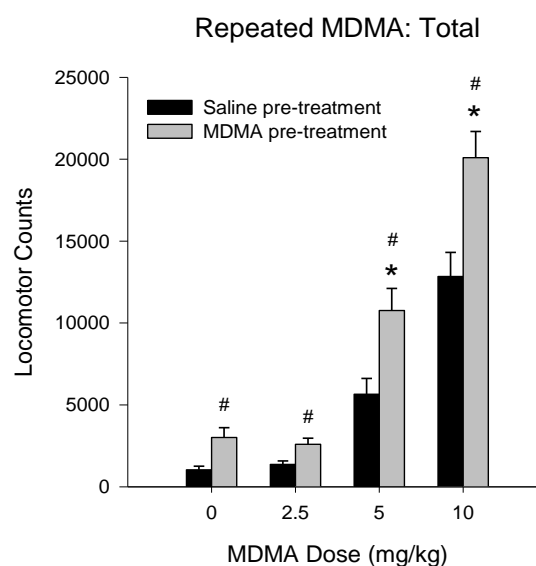


Figure 4. Effect of repeated MDMA on locomotor activity. Average total locomotor activity counts of saline pre-treated and MDMA pre-treated (10.0mg/kg) rats in the 60min following a challenge injection of MDMA (0.0, 2.5, 5.0, or 10.0mg/kg). * $p < 0.05$ vs 0.0 mg/kg dose. # $p < 0.05$ MDMA vs saline.

A significant main effect of pre-treatment was found in the centre ($F(1, 87) = 32.425$, $p < 0.0001$), periphery ($F(1, 87) = 14.506$, $p < 0.0001$), and across the open field ($F(1, 87) = 26.127$, $p < 0.05$). A significant main effect of dose was also found in the centre ($F(3, 87) = 32.508$, $p < 0.0001$), periphery ($F(3, 87) = 68.367$, $p < 0.0001$), and across the open field ($F(3, 87) = 83.020$, $p < 0.0001$).

Interactions between pre-treatment and dose were found in the centre ($F(3, 87) = 5.391$, $p < 0.01$), and across the open field ($F(3, 87) = 3.485$, $p < 0.01$). Post-hoc tests revealed significant increases in locomotion of MDMA pre-treated rats when compared to saline pre-treated rats at the 5.0 and 10.0mg/kg doses in the centre ($p < 0.0001$), periphery ($p < 0.01$), and across the open field ($p < 0.0001$). Additionally, greater locomotion is produced by AMPH pre-treatment at the 0.0 and 2.5mg/kg doses in the periphery ($p < 0.05$) and across the open field ($p < 0.05$).

Previous literature has found central-zone activity induced by MDMA to increase in sensitised rats (McCreary et al., 1999; Colussi-Mas & Schenk, 2008). To establish whether the current data found the same result, Figure 5 plots central and peripheral activity as a proportion of total locomotion for saline and MDMA pre-treated rats.

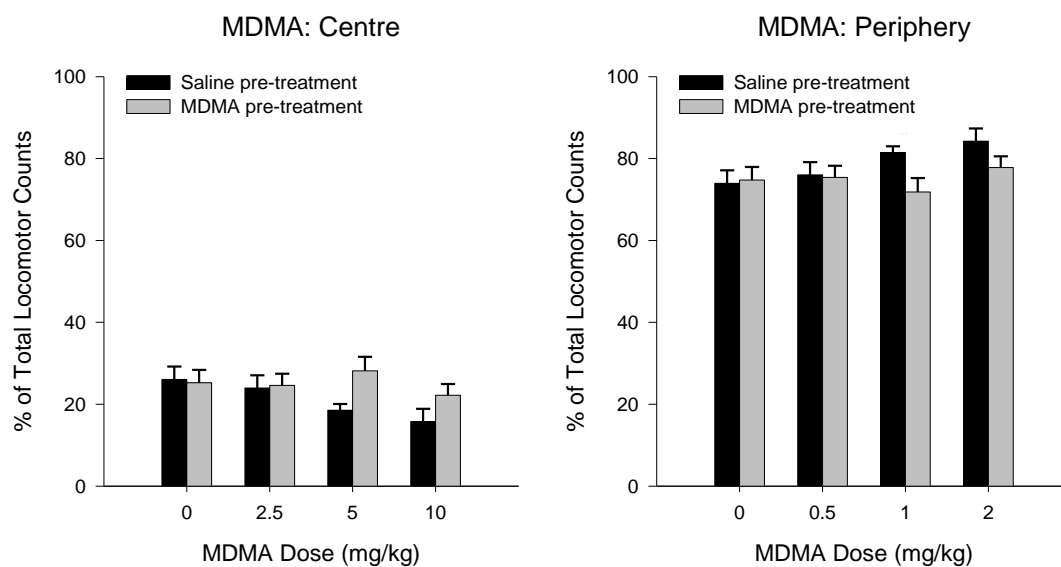


Figure 5. Centre and Peripheral activity as a percentage of total locomotor activity counts for saline and MDMA (10.0 mg/kg) pre-treated rats. # $p < 0.05$ saline vs MDMA

Though no significant results were found, the decrease in centre activity seen in saline pre-treated rats is not observed with the MDMA pre-treated rats.

Figure 6 shows the average total, centre, and periphery activity (+ SEM) during the 60 minutes following an injection of AMPH (0.0, 0.5, 1.0, or 2.0mg/kg) on the challenge day of the sensitisation regimen.

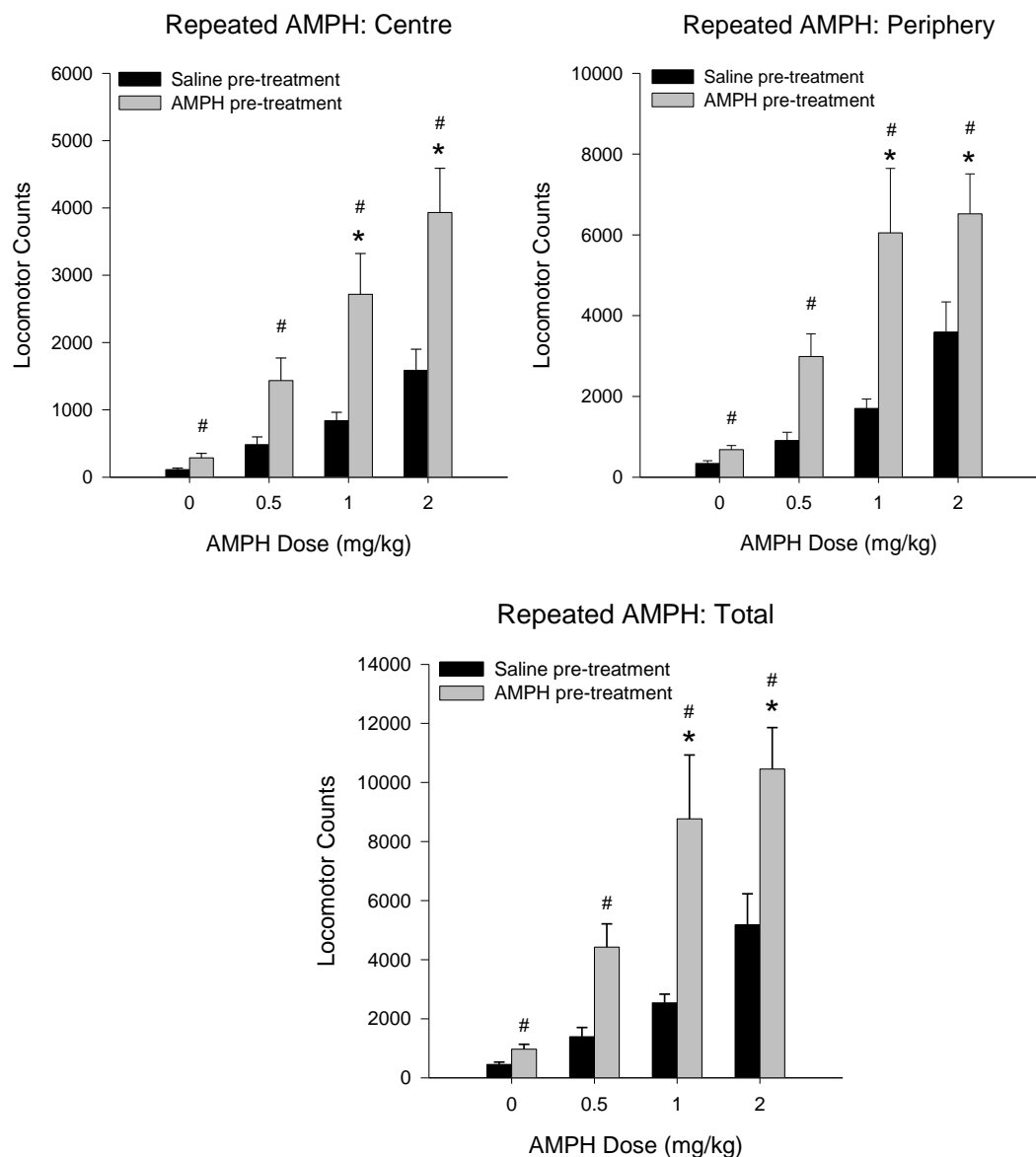


Figure 6. Effect of repeated AMPH on locomotor activity. Average total locomotor activity counts of saline pre-treated and AMPH pre-treated (2.0mg/kg) rats in the 60min following a challenge injection of AMPH (0.0, 0.5, 1.0, or 2.0mg/kg). * $p < 0.05$ vs 0.0 mg/kg dose. # $p < 0.05$ AMPH vs saline.

A significant main effect of pre-treatment was found in the centre ($F(1, 71) = 33.666$, $p < 0.0001$), periphery ($F(1, 71) = 25.910$, $p < 0.0001$), and across the open field ($F(1, 71) = 32.645$, $p < 0.05$). A significant main effect of dose was also found in the centre ($F(3, 69) = 25.554$, $p < 0.0001$), periphery ($F(3, 69) = 20.599$, $p < 0.0001$), and across the open field ($F(3, 69) = 25.458$, $p < 0.0001$).

Interactions between pre-treatment and dose were found in the centre ($F(3, 69) = 5.148$, $p < 0.01$), periphery ($F(3, 69) = 3.688$, $p < 0.05$), and across the open field ($F(3, 69) = 4.523$, $p < 0.01$). Post-hoc tests revealed significant increases in locomotion of AMPH pre-treated rats when compared to saline pre-treated rats at all doses in the centre ($p < 0.05$), periphery ($p < 0.05$), and across the open field ($p < 0.05$).

Locomotor counts following AMPH doses of 1.0 mg/kg and 2.0 mg/kg were significantly increased from the 0 mg/kg dose in the centre ($p < 0.0001$), periphery ($p < 0.0001$), and across the open field ($p < 0.0001$).

As expected, AMPH pre-treated rats produced greater locomotion to a subsequent AMPH challenge when compared to saline pre-treated rats (acute data). To evaluate the proportion of total locomotor counts produced in the centre and periphery, Figure 7 plots central and peripheral activity as a proportion of total locomotion for saline and AMPH pre-treated rats.

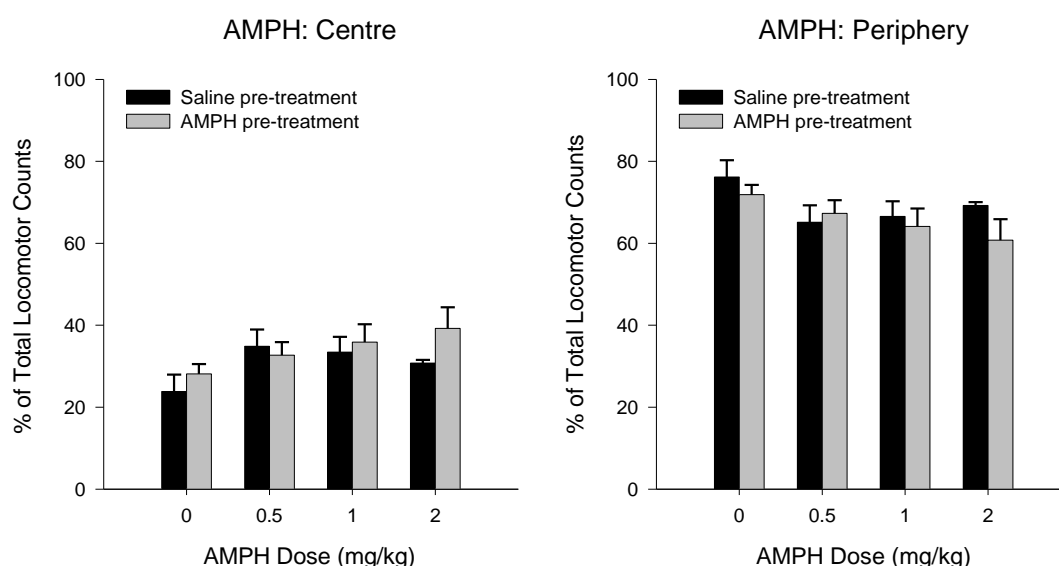


Figure 7. Centre and Peripheral activity as a percentage of total locomotor activity counts for saline and AMPH (2.0 mg/kg) pre-treated rats.

Though no significant results were found, a slight increase in central activity with dose increase can be seen in AMPH pre-treated rats. Saline pre-treated rats, however, showed a tendency to decrease central activity as AMPH dose increased.

Part III: Cross-sensitisation between MDMA and AMPH

Figure 8 shows the average total locomotor activity counts of saline pre-treated and AMPH pre-treated rats across the open-field, central, and peripheral zones (+ SEM) in the 60 minutes following an injection of MDMA on the challenge day of the sensitisation regimen.

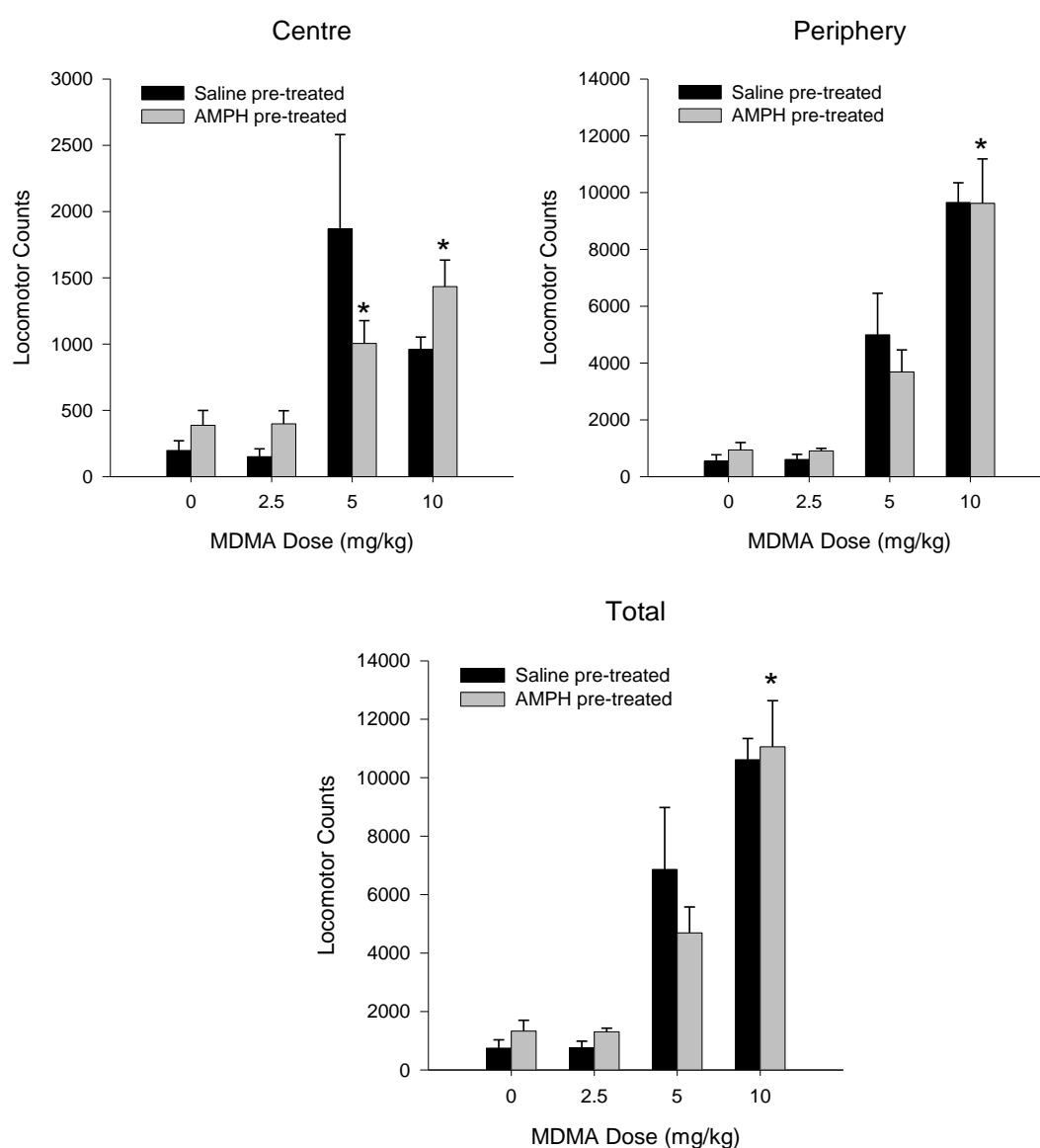
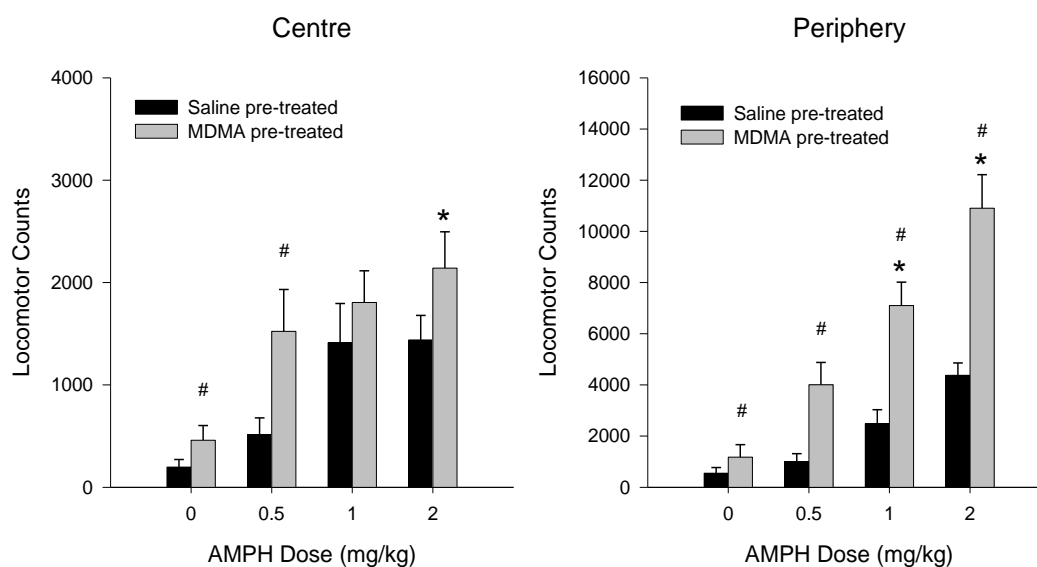


Figure 8. AMPH pre-treatment with MDMA challenge. Average total locomotor activity counts of saline pre-treated and AMPH pre-treated (2.0mg/kg) rats in the 60min following a challenge injection of MDMA (0.0, 2.5, 5.0, or 10.0mg/kg). * $p < 0.05$ vs 0.0mg/kg dose.

A main effect of dose was found in the centre ($F(3, 70) = 16.820, p < 0.0001$), periphery ($F(3, 70) = 41.388, p < 0.0001$), and across the open field ($F(3, 70) = 48.795, p < 0.0001$). Post-hoc analyses showed the 10.0mg/kg dose of MDMA to produce significantly greater locomotion than the 0.0mg/kg dose.

Figure 9 shows the average total locomotor activity counts of saline pre-treated and MDMA pre-treated rats across the open-field, central, and peripheral zones (+ SEM) in the 60 minutes following an injection of AMPH on the challenge day of the sensitisation regimen.



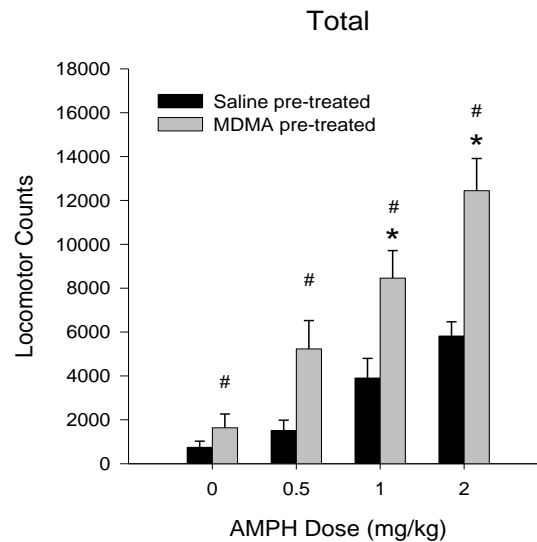


Figure 9. MDMA pre-treatment with AMPH challenge. Average total locomotor activity counts of saline pre-treated and MDMA pre-treated (10.0mg/kg) rats in the 60min following a challenge injection of AMPH (0.0, 0.5, 1.0, or 2.0mg/kg). * $p < 0.05$ vs 0.0mg/kg dose. # $p < 0.05$ MDMA vs saline.

A significant main effect of pre-treatment was found in the centre ($F(1, 61) = 13.820$, $p < 0.01$), periphery ($F(1, 61) = 69.445$, $p < 0.0001$), and across the open field ($F(1, 61) = 54.092$, $p < 0.01$). A significant main effect of dose was also found in the centre ($F(3, 59) = 14.260$, $p < 0.0001$), periphery ($F(3, 59) = 32.254$, $p < 0.0001$), and across the open field ($F(3, 59) = 29.147$, $p < 0.0001$).

Interactions between pre-treatment and dose were found in the periphery ($F(3, 59) = 8.483$, $p < 0.0001$), and across the open field ($F(3, 59) = 5.233$, $p < 0.01$). Post-hoc tests revealed significant increases in locomotion of MDMA pre-treated rats when compared to saline pre-treated rats at the 0.0, 0.5, and 1.0mg/kg doses in the centre ($p < 0.05$), periphery (0.05), and across the open field ($p < 0.05$). Additionally, greater locomotion is produced by MDMA pre-treatment at the 2.0mg/kg dose in the periphery ($p < 0.01$) and across the open field ($p < 0.001$).

Locomotor counts following an AMPH dose of 2.0 mg/kg were significantly increased from the 0 mg/kg dose in the centre ($p < 0.01$), periphery ($p < 0.001$), and across the open field ($p < 0.001$). Further, 1.0mg/kg AMPH differed from 0mg/kg in the periphery ($p < 0.001$), and across the open field ($p < 0.001$).

Part IV: Cross-sensitisation to the locomotor activating effects of the dopamine D1 agonist, SKF 81297

Figure 10 shows the average total locomotor activity counts of saline pre-treated and MDMA pre-treated rats across the open-field, central, and peripheral zones (+ SEM) in the 60 minutes following an injection of SKF (0.0, 1.0, or 2.0mg/kg) on the challenge day of the sensitisation regimen.

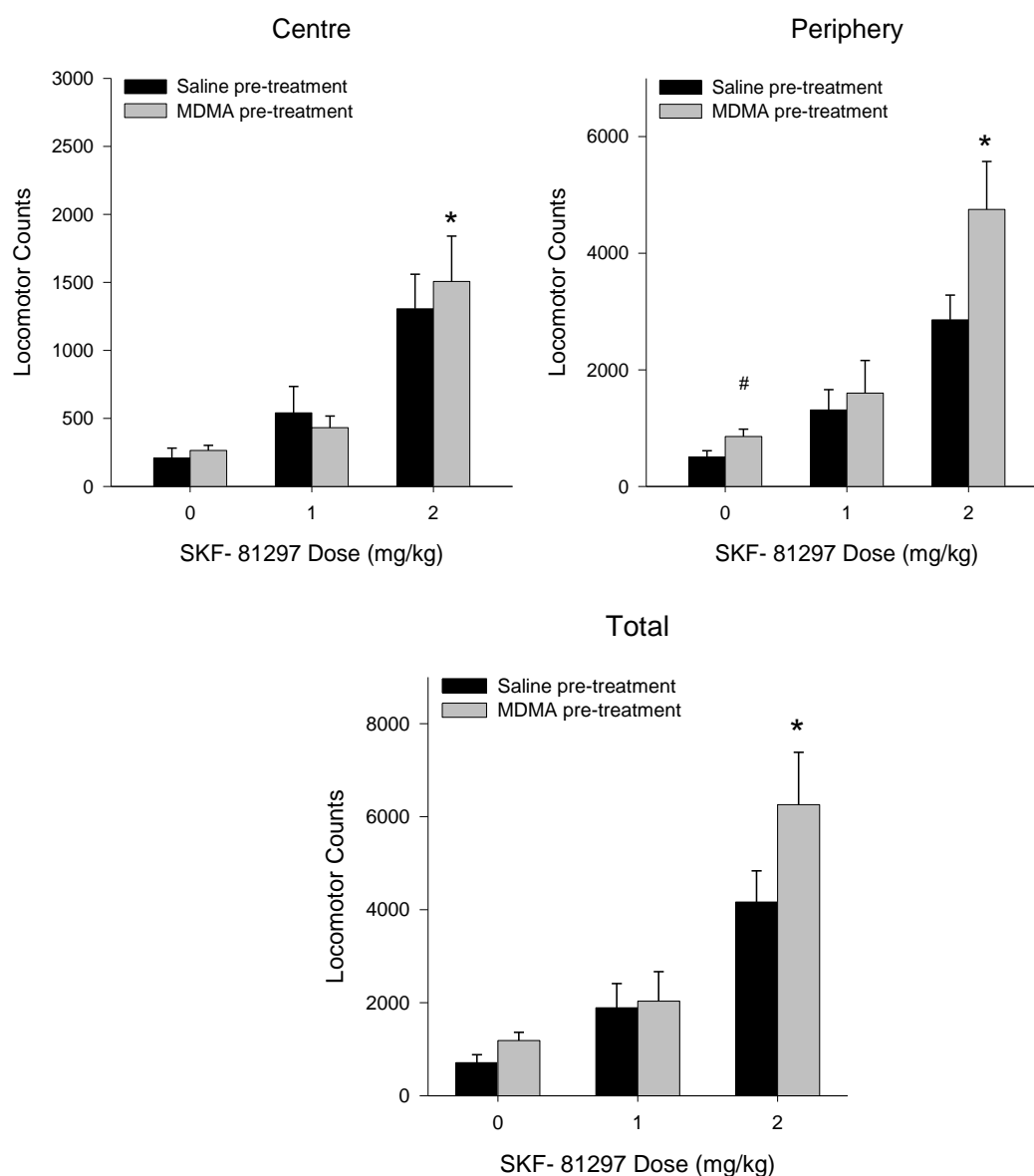
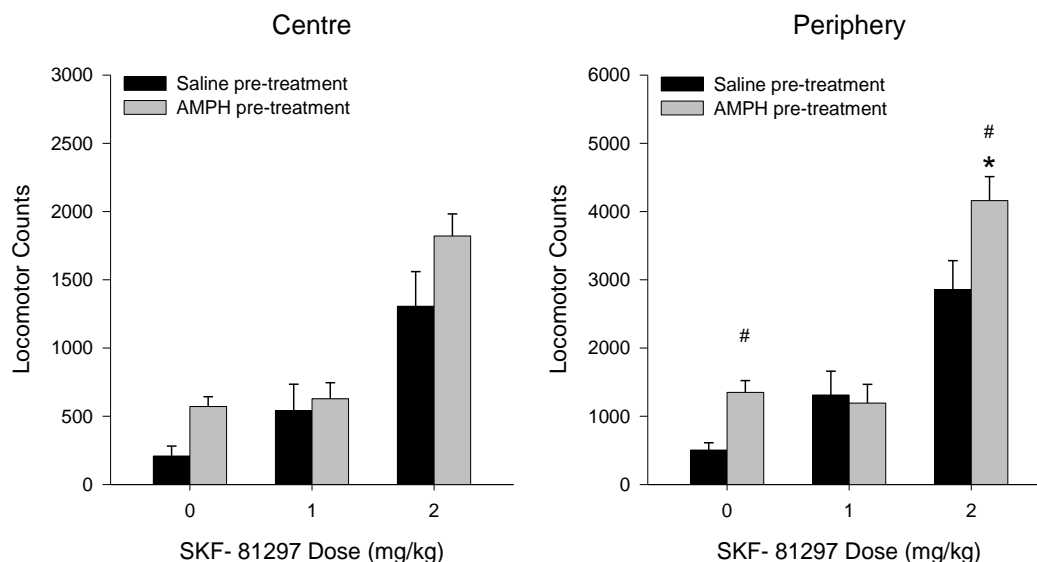


Figure 10. MDMA pre-treatment with SKF-81297 challenge. Average total locomotor activity counts of saline pre-treated and MDMA pre-treated (10.0mg/kg) rats in the 60min following a challenge injection of SKF (0.0, 1.0, or 2.0mg/kg). * $p < 0.05$ vs 0.0mg/kg dose.

A significant main effect of pre-treatment was found in the periphery ($F(2, 57) = 37.710$, $p < 0.0001$), and across the open field ($F(1, 57) = 4.111$, $p < 0.05$). A significant main effect of dose was also found in the centre ($F(2, 56) = 29.890$, $p < 0.0001$), periphery ($F(2, 56) = 37.710$, $p < 0.0001$), and across the open field ($F(2, 56) = 37.009$, $p < 0.0001$).

Locomotor counts of MDMA pre-treated rats following a SKF dose of 2.0 mg/kg were significantly increased from the 0 mg/kg dose in the centre ($p < 0.0001$), periphery ($p < 0.0001$), and across the open field ($p < 0.0001$).

Figure 11 shows the average total locomotor activity counts of saline pre-treated and AMPH pre-treated rats across the open-field, central, and peripheral zones (+ SEM) in the 60 minutes following an injection of SKF (0.0, 1.0, or 2.0mg/kg) on the challenge day of the sensitisation regimen.



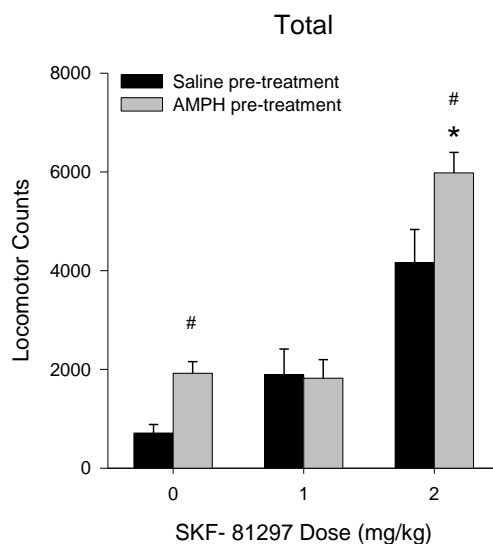


Figure 11. AMPH pre-treatment with SKF-81297 challenge. Average total locomotor activity counts of saline pre-treated and AMPH pre-treated (2.0mg/kg) rats in the 60min following a challenge injection of SKF (0.0, 1.0, or 2.0mg/kg). * $p < 0.05$ vs 0.0mg/kg dose; # $p < 0.05$ AMPH vs saline.

A significant main effect of pre-treatment was found in the centre ($F(1, 56) = 7.886$, $p < 0.0001$), with the AMPH pre-treated rats producing significantly greater locomotion at the 0 mg/kg dose. A significant main effect of pre-treatment was also found in the periphery ($F(1, 56) = 9.679$, $p < 0.01$), and across the open field ($F(1, 56) = 9.993$, $p < 0.01$), with the latter due to significantly greater locomotion at the 0 and 2 mg/kg doses.

A significant main effect of dose was also found in the centre ($F(2, 55) = 41.241$, $p < 0.0001$), periphery ($F(2, 55) = 26.649$, $p < 0.0001$), and across the open field ($F(2, 55) = 57.769$, $p < 0.0001$). Locomotor counts of AMPH pre-treated rats following a SKF dose of 2.0 mg/kg were significantly increased from the 0 mg/kg dose in the centre ($p < 0.0001$), periphery ($p < 0.0001$), and across the open field ($p < 0.0001$).

An interaction was found in the periphery ($F(2, 55) = 3.165$, $p < 0.05$). Post-hoc analyses revealed AMPH pre-treated rats produced significantly greater locomotion at the 0 and 2 mg/kg doses.

Discussion

The main objective of this thesis was to compare the neuroadaptations produced by repeated MDMA and AMPH by undertaking experiments to measure cross-sensitisation between the behavioural effects of the two drugs. Additionally, the role of D₁ receptors in mediating the sensitised hyperlocomotor response was determined. To achieve this, the behavioural profile produced by acute and repeated MDMA and AMPH was first analysed. During subsequent experiments the effects of pre-treatment with saline, MDMA, or AMPH on the acute response to MDMA, AMPH, or the D₁ agonist, SKF-81297 was measured to determine whether cross-sensitisation was produced. Based on previous literature, it was hypothesised that the profile of acute MDMA- and AMPH-produced hyperactivity would differ: MDMA was expected to produce activity predominantly in the periphery, whilst AMPH was expected to produce activity in both the centre and periphery. The behavioural profiles produced by repeated drug were, however, expected to be similar. Previous literature reported a disproportionate increase in MDMA-produced centre hyperactivity to result, comparable to AMPH, in hyperactivity across the centre and periphery.

Experiment 1 compared the acute locomotor activating effects of MDMA and AMPH. As has been previously demonstrated (McCreary et al., 1999) the profiles of MDMA- and AMPH-produced hyperactivity differed: MDMA produced hyperactivity primarily in the periphery of the open-field, whereas AMPH produced hyperactivity in both the centre and periphery of the open-field. Additionally, MDMA had greater efficacy than AMPH, as observed by the greater number of locomotor counts following MDMA administration.

The different behavioural profile of the two drugs may reflect different neurochemical effects. Dopaminergic mechanisms have been implicated in both MDMA- and AMPH-produced hyperlocomotion: both D₁-like or D₂-like antagonists attenuated MDMA- (Ball et al., 2003; Bubar et al., 2004; Daniela et al., 2004) and AMPH- (Bardo et al., 1999; Depoortere et al., 2003; Mazurski & Beninger, 1991; Mithani et al., 1986) produced hyperlocomotion; and the neurotoxin, 6-OHDA,

reduced MDMA-induced hyperactivity (Gold, Kubner, & Koob, 1989), but completely blocked AMPH-induced hyperlocomotion (Kelly & Iverson, 1976).

There are some data to suggest that pharmacological activation of different DA receptor subtypes produces hyperactivity that is consistent with the profile produced following either MDMA or AMPH. For example, the D₂/D₃ receptor agonist, quinpirole, produced locomotion at the extreme outer area of the open-field but not in the centre, a profile comparable to that observed following MDMA, but not AMPH. When a D₁ agonist was co-administered with quinpirole, locomotion was produced across a greater area of the open-field, and was not restricted to the outer extremities, a profile more comparable to that observed following AMPH (Eilam, Clements, & Szechtman, 1991). Therefore, activation of D₂ receptors might produce hyperactivity restricted to the periphery whereas activation of D₁-like receptors might be required to produce activity that is distributed across the open field. The selective D₁ agonist, A-68930, produced locomotion in both the centre and periphery (Salmi & Ahlenius, 2000) highlighting the importance of this receptor subtype in more generalised hyperactivity.

These findings suggest that activation of D₂ receptors might produce peripheral locomotion whereas activation of D₁ receptors might produce more general hyperactivity. If so, MDMA produced hyperlocomotion may be due to more selective activation of D₂ receptor mechanisms and AMPH-produced hyperactivity may be due to activation of both D₁ and D₂ receptor mechanisms. To the best of our knowledge, no one has compared centre and periphery activity following MDMA and AMPH co-administered with a D₁ or D₂ receptor antagonist. Results of such a study would, however, provide further insight into the specific receptor mechanisms underlying MDMA- and AMPH-produced hyperlocomotion.

Some data suggest that MDMA-produced hyperlocomotion may also be due to non-dopaminergic mechanisms. For example, neurotoxic 6-OHDA lesions produced thigmotaxis similar to the profile of MDMA-produced hyperactivity (Carrera, Mattioli, & Tomaz, 1992). Since 6-OHDA only

reduced MDMA-produced hyperlocomotion (Gold et al., 1989), other non-dopaminergic mechanisms might also be involved. Further, as 6-OHDA lesions produced a behavioural profile comparable to that produced by MDMA, it may be that similar non-dopaminergic mechanisms may underlie the thigmotaxic response to MDMA and 6-OHDA. Studies of the centre and periphery hyperlocomotion produced by MDMA in 6-OHDA-lesioned rats would provide further information of how dopaminergic mechanisms influence MDMA-produced hyperactivity.

Pharmacological studies suggest that 5-HT might also play a significant role in MDMA-produced hyperactivity and that the mechanisms might differ from those involved in AMPH-produced hyperactivity. Selective 5-HT_{2A} antagonists blocked both MDMA- (Kehne et al., 1996) and AMPH- (Sorensen et al. 1993; Moser, Moran, Frank, & Kehne, 1996; O’Niell, Heron-Maxwell, & Shaw, 1999; Porras et al. 2002; Auclair, Blanc, Glowinski, & Tassin 2004) produced hyperlocomotion, but only MDMA-induced hyperlocomotion was attenuated by non-selective antagonists (Layer, Uretsky, & Wallace, 1992; Fletcher, Korth, Robinson, & Baker, 2002; Hall, Powers, & Gulley, 2009). Further, selective 5-HT_{1A} or 5-HT_{1B/1D} antagonists reduced MDMA-induced hyperlocomotion (Kehne et al., 1996; Fletcher, et al., 2002), but failed to alter AMPH-produced hyperlocomotion (Layer et al., 1992). Thus, some serotonergic mechanisms seem to be common for MDMA- and AMPH-produced hyperactivity. However, the effects of MDMA appear to be more affected by specific receptor manipulations, whilst the involvement of serotonin in AMPH-produced hyperactivity may be via serotonin modulation of DA neurotransmission.

Further evidence for roles of specific 5-HT receptor mechanisms in MDMA-produced hyperactivity comes from behavioural profiles produced by selective ligands. 5-HT_{1A} and 5-HT_{2A/2C} agonists produced locomotion that was predominantly observed in the periphery of the open-field, as has been observed following acute exposure to MDMA (Hillegaart, Estival, & Ahlenius, 1996; De La Garza & Cunningham, 2000; Cannizzaro et al., 2003). Thus, in addition to DA, MDMA-produced hyperactivity may be due to these serotonergic receptor mechanisms.

MDMA- and AMPH- produced hyperactivity appears to be mediated, at least partly, by different mechanisms, which is reflected in different centre and periphery hyperactivity. Locomotion produced in the centre and periphery may also differ following the repeated administration of MDMA and AMPH as some neural mechanisms may become sensitised and others desensitised. It is well documented that behavioural sensitisation produced by repeated exposure to AMPH is due to sensitisation of DA mechanisms (see Pierce & Kalivas, 1997). According to the rationale presented above, sensitisation of D₁ receptor mechanisms would be expected to be reflected in increased activity in both the periphery and the centre of the open field, and D₂ receptor mechanisms only in the periphery.

Repeated exposure to MDMA also produces sensitised hyperactivity (Spanos & Yamamoto, 1989; Kalivas et al., 1998) but the neurochemical mechanisms that underlie MDMA-induced sensitisation are not well understood. If other mechanisms, additional to DA, contribute to sensitisation, then a preferential increase in either the centre or the periphery might be expected. Thus, if repeated MDMA and AMPH produce different neuroadaptations, one would expect different profiles of behaviour in terms of centre and periphery hyperactivity.

Experiment 2 compared the locomotor response following repeated MDMA and AMPH. As has been previously demonstrated, repeated MDMA (e.g. Spanos & Yamamoto, 1989; Kalivas et al., 1998) and AMPH (Kuczenski & Leith, 1981; Leith & Kuczenski, 1982) produced a sensitised locomotor response. The profile of the sensitised locomotor response to the two drugs was similar: both MDMA- and AMPH-induced sensitisation reflected enhanced centre and peripheral hyperactivity. The lack of sensitised hyperactivity preferentially expressed in the centre region contrasts with results found by McCreary et al. (1999), and Colussi-Mas and Schenk (2008), who reported a sensitised response driven by a disproportionate increase in centre activity. However, the current study tested a range of MDMA doses, whereas Colussi-Mas and Schenk (2008) measured the behavioural response to only one, low dose (5.0 mg/kg) of MDMA following pre-treatment. These

findings highlight the importance of completing full dose-effect curves following pre-treatment. Indeed, when all of the data were considered, the proportion of total activity spent in the centre following acute and repeated MDMA did not significantly differ and sensitisation was reflected in an increase in activity in both components of the open field.

The behavioural profile following repeated AMPH was comparable to the effect of acute AMPH; sensitised hyperlocomotion was produced in both the centre and periphery, as has previously been reported (Callaway, Wing, & Geyer, 1990). Hence, acute MDMA and AMPH produce different hyperlocomotor profiles, but repeated administration of the drugs produced similar hyperlocomotor profiles.

To investigate whether the neuroadaptations produced by repeated MDMA were similar to changes produced following AMPH exposure, Experiment 3 compared the behavioural profile of MDMA- and AMPH-induced sensitisation using a cross-sensitisation protocol. If changes associated with repeated exposure to MDMA reflected mechanisms that mediated AMPH-produced hyperactivity, it was expected that MDMA pre-treatment would produce sensitisation to the behavioural effects of AMPH. Because the acute effects of AMPH and MDMA differed, however, it was expected that repeated AMPH would not produce cross sensitisation to the effects of MDMA. The results supported the hypothesis, because cross-sensitisation was unidirectional. Thus, the data suggest that acute MDMA produces its behavioural effects through neurochemical mechanisms that are different from those activated by AMPH, but the neuroadaptations produced by repeated MDMA render the drug effects more AMPH-like.

Repeated MDMA induced sensitisation to AMPH-produced increased peripheral, but not centre, activity. Repeated exposure to AMPH, however, failed to produce sensitisation to MDMA-produced hyperactivity in either the centre or periphery. A previous study, however, failed to demonstrate sensitisation to the effects of AMPH following MDMA pre-treatment (Modi et al., 2006). The disparity in results may reflect the different protocols used: the current experiment

imposed a two day withdrawal period between MDMA pre-treatment and AMPH administration, whereas Modi et al. (2006) imposed a thirty-two day withdrawal period.

There are no studies that have directly compared sensitisation after different drug-free periods following MDMA exposure. The temporal parameters of sensitisation have, however, been studied in AMPH pre-treated subjects. For example, repeated AMPH resulted in behavioural sensitisation after both short and long withdrawal periods, but sensitised DA release was observed only after a long withdrawal period (Kolta, Shreve, De Souza, & Uretsky, 1985; Robinson, Jurson, Bennett, & Bentgen, 1988; Wolf, White, & Hu, 1993; Wolf et al., 1993; Paulson & Robinson, 1995). These findings have led to the suggestion that sensitisation during early and late withdrawal might rely on different neuroadaptations. This raises the possibility that the relevant long-term adaptations observed following repeated AMPH may not be produced following repeated MDMA. It would be interesting to investigate whether the sensitised response to acute AMPH in MDMA pre-treated animals persists after increased withdrawal periods, and such research would provide further insight into the neuroadaptations underlying the behavioural effects.

Because repeated AMPH failed to cross-sensitise to MDMA-produced hyperactivity but the reverse was produced, there must be a change in the effect of MDMA so that the neurochemical effects become more AMPH-like. Cross-sensitisation was found only in the periphery, which suggests a specific neuroadaptation. One possible neuroadaptation is a sensitised DA response (McCreary et al., 1999). AMPH-produced hyperlocomotion has been attributed to dopaminergic mechanisms (see above).

A wealth of research suggests that psychostimulant-induced sensitisation is due to neuroadaptations within the mesocorticolimbic DA pathway. Because repeated MDMA and AMPH both produced sensitised centre and periphery activity, a behavioural profile that was also observed following D₁ agonist administration, Experiment 4 addressed the role of D₁ receptor mechanisms in the behavioural expression of sensitisation. The results suggest that D₁ receptor mechanisms are

differentially affected by repeated MDMA and AMPH. Repeated MDMA failed to produce a sensitised response to the D₁ agonist, SKF-81297. In contrast, repeated AMPH produced sensitisation to SKF-81297-produced hyperactivity in the periphery. Thus, it appears that repeated exposure to MDMA and AMPH result in different neuroadaptations in D₁-like responses.

A small number of studies has investigated the role of D₁ receptor mechanisms in the expression of MDMA- and AMPH-induced sensitisation, and, of those, only two that we are aware of have used systemic administration of DA ligands. In one study, however, repeated AMPH failed to sensitise rats to the locomotor-activating effects of the D₁ agonist SKF-82958 when administered following a twenty-one day drug-free period (Vanderschuren et al., 1999). The disparity in results may reflect differential contribution of D₁ mechanisms in short- and long-term sensitised responses.

The lack of a sensitised response to SKF-81297 following MDMA pre-treatment suggests that MDMA-induced sensitisation does not require sensitised D₁-like receptors. D₁ receptor mechanisms are implicated in the expression of the sensitised response, however, because the D₁-like antagonist, SCH 23390, attenuated the expression of sensitisation to MDMA-produced hyperactivity (Ramos et al., 2003). Alternatively, the effects of SCH 23390 might be due to blockade of 5-HT_{2C} receptor mechanisms, because the administration of the 5-HT_{2C} antagonist RS-102221 reversed the SCH-23390-induced blockade of the expression of the sensitised response (Ramos et al., 2005).

Localised infusion studies have indicated VTA D₁ receptor mechanisms may be implicated in AMPH-induced behavioural sensitisation (Vezina, 1996). However, no previous research has examined whether VTA D₁ receptor mechanisms may also play a role in MDMA-induced sensitisation. Such a study, in which MDMA pre-treatment is administered locally into the VTA, followed by a systemic administration of a D₁ antagonist, would be of interest. The failure of the antagonist to have an effect on MDMA-produced behaviour would suggest different neuroadaptations are produced by repeated MDMA and AMPH.

In addition to the effects on D₁ receptor mechanisms, repeated MDMA and AMPH may produce differential effects on D₂ receptor mechanisms. To the best of our knowledge, the behavioural effects of D₂ receptor mechanisms have not been investigated with repeated MDMA. However, following repeated exposure to AMPH, systemic D₂/D₃ receptor agonists produced a sensitised locomotor response (Chen, Su, Huang, & Hsieh, 1998; Vanderschuren et al. 1999). Clearly, research must be undertaken to investigate the behavioural effects of D₂ receptor manipulations following repeated MDMA to compare the contribution of D₂ receptor mechanisms in the behavioural profile of MDMA- and AMPH-induced sensitisation.

Further to dopaminergic transmission, differences in serotonergic transmission may underlie the different neuroadaptations. The role of serotonergic transmission appears to differ in producing acute MDMA and MDMA behavioural effects; however, very little research has addressed the role of serotonergic receptor mechanisms in psychostimulant-induced sensitisation. The systemic administration of the 5-HT_{1B/1A} agonist, RU-24969, in MDMA pre-treated animals produced a sensitised locomotor response found predominantly in the periphery of the open-field (McCreary et al., 1999). Thus the profile of locomotion produced by MDMA and RU-24969 in MDMA pre-treated rats is similar. Therefore, 5-HT_{1B/1A} receptor-mediated mechanisms may be involved in the expression of MDMA-induced sensitisation. However, to the best of our knowledge, no further research has been completed using serotonergic ligands to assess the neurochemistry underlying MDMA- and AMPH-induced sensitisation. Therefore, further research of the effects of 5-HT receptor ligands on repeated MDMA- and AMPH-produced hyperactivity needs to be undertaken to ascertain the role of serotonergic receptor mechanisms in MDMA- and AMPH-induced sensitisation.

A disparity was found in behavioural profiles produced by acute MDMA and AMPH, suggesting different neural mechanisms. However, the disparity was not apparent following repeated exposure to the two drugs. Specifically, the profile of MDMA-produced hyperactivity became more AMPH-like. Indeed, repeated MDMA resulted in a sensitised response to AMPH-

produced peripheral activity, suggesting a specific neuroadaptation produced by the repeated MDMA that also underlies AMPH-produced peripheral activity. AMPH pre-treatment produced a sensitised response in the periphery to the D₁ agonist SKF-81297, suggesting D₁ receptor mechanisms underlie AMPH-induced sensitisation or periphery activity. However, MDMA pre-treatment did not produce sensitisation to the locomotor-activating effects of SKF-81297, suggesting D₁ receptor mechanisms are not sensitised following repeated MDMA. Further research of the different neuroadaptations produced by repeated MDMA and AMPH should investigate the roles of D₂ and serotonergic receptor mechanisms in producing centre and periphery sensitised behaviour.

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