The Acute Effects of Methamphetamine and 1-Benzylpiperazine on Aggressive Behaviour in Adolescent Male Hooded Rats

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Abbreviations

ANS	Autonomic Nervous System
BZP	1-benzylpiperazine
CNS	Central Nervous System
DA	Dopamine
IDMS	Illicit Drug Monitoring System
LTA	Latency Time to Attack
MA	Methamphetamine
Mg/kg	Milligrams Per Kilogram (drug dosage)
NA	Nucleus Accumbens
n=	Number
PND	Post Natal Days
PFC	Pre Frontal Cortex
5-HT	Serotonin
SEM	Standard Error of the Mean
SNS	Sympathetic Nervous System

Abstract

Violent crime and aggressive behaviour are of increasing concern in New Zealand. Much of this is displayed by adolescent males who have an association with some form of substance use, abuse or dependence. This is especially relevant for stimulant drugs, especially methamphetamine (MA), and 1-benzylpiperazine (BZP). Previous research has shown that BZP has similar neurochemical and behavioural effects to MA, and there is a large volume of research showing an association between chronic MA use and aggression. In contrast to this, there has been little research into the consequences of a single administration of MA, which is often portrayed by the media as having the same detrimental effects as chronic use.

The present study was designed to determine whether or not acute MA would induce aggressive behaviour in adolescent male hooded rats. In addition, the study also examined whether BZP had a similar effect to MA. Sixty male hooded rats aged between 41 to 50 postnatal days (PND), were utilised and divided into five groups of 12 rats each: saline; 1mg/kg (low dose) or 2mg/kg (high dose) MA; 10mg/kg (low dose) or 20mg/kg (high dose) BZP. The rats were tested using the resident/intruder test of aggression, consisting of eight measures of aggressive behaviour. The results suggested that, rats treated with either a low or high dose of MA or BZP were significantly less aggressive than saline-treated rats. There appeared to be little to distinguish between the two drugs in their effects on the responses recorded. It was concluded that an acute administration of either MA or BZP did not increase aggression, and thus did not support the view that aggression will result from a single dose of MA (or indeed BZP that has not been previously investigated in this context).

1.0 Introduction

1.1 General Introduction

The issue of increasing acts of violence and aggression in New Zealand, as in the rest of the world, is a major concern for society as a whole (Fergusson, Boden, & Horwood, 2008; Miczek, Fish, de Bold, & de Almeida, 2002; Weinshenker, & Siegal, 2002). The resulting costs to victims, the public and even the perpetrators themselves are significant, and of detrimental value to society. These detrimental costs include monetary - from court costs, imprisonments and police hours - to the more personal issue of injury (both psychological and physical) of the victim and those close to them. Of increasing relevance is the more serious violent and aggressive crime, which carries more serious and invasive consequences to both the victims, and the perpetrators themselves (Sokolov & Cadet, 2006). When examining crime in New Zealand, statistics show that crime in general is increasing with recorded crime having risen from 396,018 recorded crimes (963.4 per 10, 000 people) in 2004/2005 to 442,540 recorded crimes in 2008-2009 or 1031.9 per 10, 000. When breaking these statistics down to isolate violent crime, a similar pattern emerges with an increase from 2004/2005 to 2006/2007 when violent offences made up 12.4% of total crime (52,892, or 125.7 per 10, 000). In 2008/2009 this had risen further to account for 14.2% of total crime (62, 874 or 146.6 per 10, 000, Police National Headquarters, 2009). These figures may appear small as a percentage, but when aspects such as personal grief and other consequences of violence and aggression are taken into account, any number is significant.

Of note is that most violent and aggressive crime is being committed by young males who have an association with some form of substance use, abuse or dependence (Armstrong & Costello, 2002; Fields & McNamara, 2003; Pellegrini, 2002). This association has long

been acknowledged as causing these more violent or aggressive responses, and is supported by an extensive volume of literature on the relationship between stimulant substances and aggressive behaviour. This is especially so for stimulant substances, which increase behavioural activity, and include cocaine and the amphetamines. Due to its more inaccessible nature, New Zealand is not influenced by the use of cocaine in comparison to other countries, but stimulants such as methamphetamine (from here on referred to as MA) are more readily available, produced and used here by offending young people. Because of this, research into aggressive behaviour resulting from the use of MA is of more relevance and importance to New Zealand than research into other stimulants such as cocaine. But what needs to be acknowledged is that, although there is a general acceptance of an association between drug use and aggression and violence, the relationship is not a simple causal one as many other factors can influence this association.

There is conflicting evidence regarding the issue of whether or not chronic or acute doses of MA are related to aggression. In particular, there has been very little research into the consequences of a single administration. Of all the studies examined by the present author, only one concluded that an acute dose administered to rats resulted in aggressive behaviour (Crowley, 1972). This was in comparison to studies of chronic use in both animals and humans which concluded there was a relationship between MA use and aggression. Especially important is the fact that MA use is portrayed by the media through news bulletins and internet websites (Tyner & Fremouw, 2008) as being an absolute for causing aggression, often suggesting that even a single experience with this drug will lead to dependence and behaviour change.

A commonly used drug that is similar to the effects of MA, both neurochemically (Baumann et al., 2005) and behaviourally (Herbert & Hughes, 2009), is 1-benzylpiperazine (BZP). This drug is the principle ingredient of ‘party pills’ (STANZ, 2005) and was only

recently reclassified in New Zealand as a restricted substance in the same general category as the amphetamines. Given the similarities between MA and BZP, it is not inconceivable that BZP might also increase aggressive behaviour, but to date there is little research showing the detrimental effects of its use.

Compounding the issue of how these two drugs may affect aggression is the problem of the media and how they portray these substances and the detrimental effects of using them. According to popular belief, which is highly influenced by the media, someone who takes MA once is then addicted, and hence prone to all the detrimental effects associated with chronic use or addiction (Tyner & Fremouw, 2008). Throughout New Zealand schools there are antidrug use campaigns in which it is stated that a single experience of MA can turn one into an aggressive person, even though there is very little research to support this stance. BZP is of less interest to the media, but this may be a result of the lack of knowledge surrounding the drug and its detrimental effects.

An understanding of how these two drugs may influence adolescent aggressive behaviour might help to reduce the associated crime and detrimental consequences experienced by victims and the perpetrators themselves. Furthermore, intervention during adolescence might reduce the chances of adult use and abuse and the incidence of associated aggressive behaviour. An important consequence of such research could be the better understanding of this complex relationship. This could then result in the reduction of the significant costs associated with adolescent crime committed while under the influence of, or dependence on a substance.

1.2 Aggression

Consistent with the need for sound scientific research on aggression, there has been a noticeable increase in research in this area. This has been directed towards the better

understanding of the origin, classification, underlying mechanisms, and treatment of the aggressive behaviour that makes up the state of aggression (Hinshaw & Lee, 2003). It is generally accepted that the concept of aggression is multidimensional and difficult to define and measure, with no universal language that enables consistent communication of findings (McEllistrem, 2004). However, it is important to overcome these deficiencies because aggression is a huge problem for public health and criminal justice (Cohen, Hsueh, Russell, & Ray, 2006; Hoaken & Stewart, 2003; Miczek et al., 2002; Parrott & Giancola, 2007; Ramirez, 2003; Weinshenker & Siegal, 2002). Parrott and Giancola (2007) add that because aggression can be expressed behaviourally in a myriad of ways, current research suffers from limitations in measurement, known as the criterion problem. This is the issue of variation between individuals in the way they behave and the difficulty researchers have in incorporating all these variations into one construct such as aggression (Austin & Villanova, 1992).

Another problem in the research on aggression and violence is that the two terms are often used interchangeably in studies that have been published. It is generally agreed that aggression is an empirical term; a verifiable behaviour based on biology, whilst violence is a social construction that is very difficult to measure by experimentation, and is influenced by cultural, environmental and social aspects (Weinshenker & Siegal, 2002). Violence would involve the concept of aggression, and aggressive responses that result from this state.

Another view is that aggression and violence are on a continuum with violence as an extreme form of aggression (Hoaken & Stewart, 2003; Ramirez, 2003). Ramirez also states that even though biology is an important factor, other aspects must also be acknowledged. Furthermore, as with other species, humans may have inherited a biological basis for aggression as a means of protection in their striving for survival. The difference with humans

is that they have a unique capability for intelligence and learning which can be applied to behaviour (Ramirez, 2003).

When attempting to define aggression, there is agreement that it usually pertains to the actions of a person towards another with the intention of causing physical or mental harm (McCormick & Smith, 1995; Weinshenker & Siegal, 2002). Most researchers agree that aggression involves the goal-directed, intentional behaviour of harming another person who perceives this behaviour as aversive and is motivated to avoid it (Hoaken & Stewart, 2003; Miczek et al., 2002). The idea of intention is important because it highlights the role of cognitive components, and their possible dysfunction through the effects of drugs (Hoaken & Stewart, 2003). It is also accepted that the neurochemicals involved in aggression include dopamine (DA) and serotonin (5-HT). Drugs that target D_2 receptors facilitate aggressive behaviour in both animals and humans (Miczek et al., 2002; McEllistrem, 2004), whereas drugs that act on 5-HT exert an inhibitory action on the responses (McEllistrem, 2004). It is acknowledged that the results of research on DA are mixed, but importantly there appears to be an interaction between the effects certain substances have on these two neurotransmitters and their relationship with aggression.

Aggression has been divided into various subtypes. For example, Parrott and Giancola (2007) regard aggression as a behavioural process that needs to be distinguished from related constructs such as hostility and anger. It is possible to feel angry or hostile, but not engage in aggressive behaviour, yet it is very difficult to act aggressively without feeling angry or hostile. To act in this latter way involves the concept of psychopathy, which is a rarer and serious personality type (Frick, Cornell, Barry, Bodin, & Dane, 2003; Hare, & Mcpherson, 1984). Separating out these different terms will help to better understand the concept of aggression and how it develops. Parrott and Giancola (2007) state that there can be ***hostile*** aggression (goal directed) and ***instrumental*** aggression (infliction of pain being the intent of

the behaviour) as well as *proactive* (bullying, threatening) or *reactive* (retaliatory), and direct or indirect/relational. Aggression can also be verbal or physical. Physical aggression is especially important, because as development progresses to adolescence, this type of aggression can become violent and assaultive, which often has more detrimental outcomes for the victims (Hinshaw & Lee, 2003; Weinshenker & Siegal, 2002). Other subtypes of aggression are *inter-male*, *irritable* (resulting from influences such as intense heat, hunger and thirst), *sex-related*, *predatory* and *territorial.* Many of these subtypes are evident in the resident/intruder aggression test where an intruder rat is placed into the home cage of a resident rat (Weinshenker & Siegal, 2002). Other researchers use *competitive* aggression, which is similar to *inter-male* because of the desire to be the best, dominant male. This competitive/inter-male aggression occurs between two males, and is very common in the animal kingdom, and is relevant to humans because of the high frequency of violent acts involving at least two males. Whatever the label or subtype an aggressive response is assigned to, all types of aggressive behaviour commonly occur when two males are placed in close proximity to each other, because of this possible inherent tendency to be the dominant male (Weinshenker & Siegal, 2002).

All of these definitions can be incorporated into the concepts of *affective defence* and *predatory attack*. There is considerable agreement that most definitions can fit under these two categories, and that much animal and human aggression contains affective or predatory characteristics. In addition, using these two categories will help to link human and animal research together, while also leading to new investigations (Weinshenker & Siegal, 2002). Subtypes such as *fear-induced*, *inter-male*, *irritable*, *sex-related* and *territorial* aggression are incorporated under *affective defence* because they all share the common feature of being an aggressive response based upon the presence of elements of fear and/or threat that are either real or perceived (Weinshenker & Siegal, 2002). McEllistrem (2004) supports the *predatory*

and *affective* aggression classification, and adds that the terms are used throughout the social, forensic, clinical and biopsychological literature, and that both neurochemical and anatomical studies support this classification. This classification of aggression incorporates and acknowledges both biology, through unique physiological substrates, and phenotypic expressions of aggression, which is the behavioural expression that results (McEllistrem, 2004). Parrott and Giancola's (2007) subtypes of aggression also fit into these two subtypes; *hostile* aggression involves affective and impulsive aggression, and is an unplanned act intended to harm another, whereas *instrumental* aggression is a premeditated act where the primary goal is to obtain some other incentive, and fits with *predatory attack*.

Predatory attack appears to be less common and, in humans, may possibly be related to rarer forms of psychopathy, and hence more difficult to measure, whilst *affective defence* is common to both humans and animals so is easier to measure and understand.

1.2.1 Affective Defence

The concept of *affective defence* has been used in research and published studies over the past 40 years, and is defined in both human and animal literature as an aggressive response based on the presence of elements of either fear and/or threat, which may be real or perceived, and has the goal to reduce or eliminate threat and thus reduce tension (Weinshenker & Siegal, 2002). In animal research this type of aggression occurs in the presence of another animal that is perceived to be a threat and has basic elements like piloerection, paw strike, shrinking or lowering of body. Research related to human behaviour, deals with *affective defence* for which the goal of reducing or eliminating threat and reducing tension is related to episodic control characterised by an explosive personality in the absence of impulse control (Weinshenker & Siegal, 2002). Researchers believe that this behaviour in humans is often associated with psychiatric problems such as paranoia and altered perceptual

states, and is believed to be a response to stimuli that evoke anger and fear (Weinshenker & Siegal, 2002). Also in support of the *affective defence* subtype is the fact that many psychometric tests (such as the Buss-Durkee Hostility Scale and the Overt Aggression Scale) are designed to measure aggression of this type because it is easier to measure than predatory aggression (Weinshenker & Siegal, 2002).

To better understand the link between substance abuse and aggression in adolescents, it is necessary for there to be agreement on the definitions and possible subtypes of aggression. This would provide more consistent and reliable results in the research. Therefore, this present study will examine the *affective defence* subtype of aggression.

1.3 Adolescence and Violence/Aggression

There is a general consensus that adolescence is a transitional phase in development during which major physical and psychological changes occur that result in a very different behavioural repertoire from what was previously characteristic (Ramirez, 2003; Smith, 2003; Spear, 2007a). From a biological perspective, adolescence is a time of considerable neural development in the brain. Areas such as the mesocorticolimbic region and the pre-frontal cortex (PFC) are especially important because of the numerous changes in DA production and utilisation that occur there. This is in addition to these areas of the brain being part of the circuitry critical for modulating risk behaviour and social behaviour, and for attaching motivational relevance to natural rewards and drugs (Spear, 2007b). This period of change and experimentation involves the use of illicit substnces, which is a common aspect of adolescence (Baskin-Sommers, & Sommers, 2006; Chambers, Taylor & Potenza, 2003; Smith, 2003; Spear, 2007b). Smith (2003) states that adolescence is a time when young people are particularly vulnerable to substance abuse and that the effects these drugs have on the developing brain are different from those for adults. The different effects for adolescents

in comparison to adults is especially so for MA thereby making them a clinically challenging population (Clingempeel, Britt, & Henggeler, 2008).

The use of substances during adolescence has been shown to be related to a number of psychiatric problems including low self esteem, anti-social behaviour, and later, more serious drug use and abuse, crime and aggression (Armstrong & Costello, 2002; Stansfield & Kirstein, 2005). Lansford, Erath, Yu, Pettit, Dodge and Bates, (2008) support and provide evidence for these short and long term problems associated with substance use in adolescence, stating that previous research links substance use with externalising disorders which include aggressive behaviour and violence. From the results of their study involving 585 young people in the Child Development Project, it was concluded that substance use disorders were more common with externalising disorders like aggressiveness than internalising disorders like depression at age 18. In a review by Armstrong and Costello (2002), it was found that 60% of young people with a substance use, abuse or dependence problem also had a co-morbid psychiatric diagnosis. They stated that child psychopathology was strongly associated with early onset substance use and abuse in late adolescence. A study in New Zealand supported this finding of child psychopathology being associated with substance use problems in adolescence. This study reported that illicit drug use from the age of 16 to 25 was associated with a wide range of early life circumstances such as parental use of illicit substances, gender and conduct problems. Being exposed to parental substance use, being a male and having co-morbid conduct problems greatly increased the chances of substance use problems in adolescence (Fergusson et al., 2008). In addition, the highest rates of referral to mental health services for this age group involve aggressive acting-out patterns of behaviour (Hinshaw & Lee, 2003).

The increasing interest in the alarming rates of violent and aggressive acts, including murder, committed by adolescents has resulted from notorious instances of youth violence in

recent years (Fields & McNamara, 2003; Pellegrini, 2002). The mean age of perpetrators is reported to be declining, and many different reasons have been proposed for why youth violence is increasing. These reasons include *social learning*, where a young person may learn aggressive behaviour by observing a parent behaving the same way; and, *attribution*, where they may make unfounded assumptions about another's intentions so that they are malevolent or cruel. This aspect may relate to the adolescent's changing cognitions during this period as well as the cognitive changes induced by substance use leading them to misinterpret the intentions of others. Other reasons include *resilience*, *developmental* and an *eclectic* view. This eclectic view for why youth violence is increasing involves a combination of all the other reasons, and incorporates substance use. This inclusion of all aspects acknowledges the great complexity of understanding why behaviour occurs.

New Zealand statistics on youth offending describe a noticeable increase in the number of youth apprehensions for violent offences over the period 1995 to 2006. In 1995 there were 2,690 violent offences, which increased to 3,743 violent offences in 2006. This equated to an overall increase of 39%. For the 2006 year, 24% of all prosecuted cases involved a violent offence (1,486 violent offences out of 6,202 offences), and across all age groups approximately one in seven apprehensions made by Police was of a 14 to 16 year old. This equated to 30,451 apprehensions of this age group out of a total of 203,484 apprehensions across all groups. In just one year from 2005 to 2006 there was a 9% increase in violence offences, which was reported to be due to a large increase in recorded grievous or serious assaults (1,324 apprehensions to 1,512). Also of note is that between 77% and 80% of these apprehensions were by male youth (Chong, 2007). This overwhelming statistical evidence for the problem of adolescent crime and violence, in combination with the acknowledged changes in brain functioning supports the need to understand why this problem exists for this

age group. Therefore, the present study will focus on this age group in the hope of adding to our understanding of how drugs affect the group.

1.4 Aggression and Substance Abuse

There is abundant research supporting the link between aggression and substance abuse, and highlighting its subsequent cost to those involved. There is consensus that the links between psychoactive substances and violence or aggression involve many different factors, including social, economic, psychosocial, psychological and biological influences. These are the processes that underlie all human behaviour, but the relationship is complex, and it is often more suggestive, than conclusive, emphasising the complexity of the relationship (Boles & Miotto, 2003; Friedman, 1998; Grimes, Ricci, Rasakhan, & Melloni Jr, 2006; Hoaken & Stewart, 2003; Homer, Solomon, Moeller, Mascia, DeRaleau, & Halkitis, 2008; McKetin McLaren, Riddell, & Robins, 2006; Sokolov & Cadet, 2006; Sokolov, Schindler, & Cadet, 2004). In addition, to date there has been very little research into this relationship in adolescents (Grimes et al., 2006).

Hoaken and Stewart (2003) divided the direct ways drugs can affect the user into three categories. Firstly: direct pharmacological effects (intoxication), secondly: neurotoxic, which involves damage to the brain and neurotransmitters from prolonged use, and thirdly: withdrawal. These researchers have also subdivided intoxication into four physiological effects that are likely to increase the chances of aggression. The first of these is: alteration of the psychomotor system. This results in the enhancement of excitation and reward, such as an increase in approach, sensation seeking and/or attack responses which would not otherwise be performed. Psychomotor stimulant properties therefore appear to potentiate violence by means of amplifying behaviour which could be characterised as risky, such as approach and engagement. The second effect is alteration of the anxiety and/or threat system, and the third

is alteration of the pain system. *Affective defence* is an unconditioned response, so drugs that heighten pain sensitivity would therefore increase the likelihood of defensive aggression. Lastly, the fourth effect is alteration of certain higher order cognitive capacities. The alteration in the ability to formulate behavioural strategies is an example of the fourth effect (Hoaken & Stewart, 2003). This alteration of higher order cognitive capacities also includes changes in mood and feelings of anxiety, which could help to result in aggression through a person's heightened state of arousal, and thus involves the flight and flight mode of response. Fight mode if activated would logically include aggression and possibly violence, and is supported by a number of results (Cancela, Basso, Martijena, Capriles, & Molina, 2001; Craske & Barlow, 2008; He, Xu, Yang & Li, 2005; London, Simon, Berman, Mandelkern, Lichtman, Braman, et al., 2004).

Because substance abuse occurs in many different contexts, the relationship between aggression and substance use is also moderated by many different factors in both the individual and the environment. Each of these different factors can influence the potential for violence or aggression to manifest itself in a person's behaviour. This leads to the problem of inferring causality to a single aspect, which is a weakness in the research on this relationship (Seddon, 2000). In addition, violence or aggression can occur at different stages of drug use, from acute intoxication, to dependence, to drug seeking behaviour. Such behaviour is associated with alleviating the unpleasant symptoms of withdrawal and, in the case of stimulant use, episodes of drug-induced psychosis and paranoia (Boles & Miotto, 2003). Seddon (2000) reported that most researchers use uni-directional mechanistic 'cause-and-effect' models. Three of the most commonly used models to understand the relationship between substance abuse and aggression and/or crime are: 1) drug use leads to crime 2) crime leads to drug use 3) both are related to other factors. Acknowledging that all three models, or aspects of each, may play a role in this relationship, acknowledges the problem of causality.

It is difficult to infer that there is a single mono-directional cause for drug use leading to crime. This mono-directional concept of the relationship has support throughout the published research (Wilkins, Griffiths, & Sweetsur, 2009). Wilkens et al. (2009) state that if there was indeed a bi-directional cause of drug use leading to crime, there would be no crime if drugs were freely available. Clearly this is not the case, meaning that researchers must acknowledge that there are other factors playing a role in the substance abuse/aggression/crime relationship, which is therefore better classed as an interactive relationship. This view fits with Goldstein (1985, cited in Boles & Miotto, 2003) who states that there are three ways that substance abuse is related to aggression or violent acts, for which there is support (Tyner & Fremouw, 2008). The first is *Psychopharmacological Violence* – where the aggressive behaviour is performed whilst under the intoxication of substances. This violent behaviour can occur through changes in brain functioning resulting from both short and long term use of drugs that produce irritability, excitability, paranoia or violent behaviour. This is the biological aspect of the relationship between drug use and aggression. The biological links between psychoactive substance abuse and violence or aggression differ by the type of drug, amount, and pattern of use (Boles & Miotto, 2003; Friedman, 1998), and incorporates Hoaken and Stewart's (2003) aforementioned ways that drugs can effect a user, as well as including the four physiological effects of intoxication.

This type of violence also includes changes or impairments in cognitive functioning resulting in the misinterpretation of the intentions of others. This can be impacted upon by intensified emotional states which relate to high and low mood, and increase in DA and reduction of 5-HT, or disruptions of hormonal or physiological functions that motivate or restrain violence (Friedman, 1998). Friedman (1998) states that the psychopharmacologic dimension involves effects on behaviour like excited, irrational violent impulses or a direct

biological effect on the structure of the brain, or a temporary physiological effect on the brain function that causes cognitive dysfunction i.e., misinterpret others' actions.

Although it is undeniable that biological factors alone do not cause violence, it is also very clear that some do play a major role in the aetiology of aggression. As stated, the neurotransmitters frequently cited as the key biological correlates of aggression are 5-HT, and DA, and it is clearly shown that stimulant substances affect these neurotransmitters (Anderson, 2005; Boles & Miotto, 2003; Bondar, & Kudryavtseva, 2005; Couppis, & Kennedy, 2008; Higgins & Katz, 1998; Julien, 2001). Low 5-HT is the most cited factor in the research, but this is probably an over simplification, as the issue is believed to be more complex than just a depletion of 5-HT, and is possibly more predictive of impulsive disturbances, depression or anxiety (Boles & Miotto, 2003). DA is involved not only with the pleasurable effects of taking a drug, but also behavioural regulation so this neurotransmitter might play a part in modulating human aggressive behaviour (Boles & Miotto, 2003). It is important to note that drugs affect the functioning of these transmitters, thereby possibly causing a confused person to experience many different emotions and cognitions.

The second way substance abuse is related to aggression or violent acts is *Systemic Violence. Systemic violence* refers to the aggressive responses displayed during the interaction within the system of drug distribution and use. An example of this type of violence is a murder or assault resulting from conflict over drug turf. The resulting threat of violence to the public creates environments of fear and intimidation for many communities (Hinshaw & Lee, 2003). In New Zealand people recently apprehended and detained in watch houses that participated in a programme for measuring drug and alcohol use said that selling amphetamines (including methamphetamine) involved the most risk and was perceived to be the most violent drug market **(**Hales & Manser, 2007; Wilkens, Girling, Sweetsur & Butler, 2005).

The third way substance abuse is related to aggression or violent acts is *Economic Compulsive Violence*. This way is related to the acquisition of drugs and the money needed to sustain a habit, which in some cases can reach very expensive proportions rapidly. There is significant overlap between all three types, and in support of systemic and economic compulsive violence is the fact that it is inevitable that criminal activity will occur within the black market world of drug trading (Tyner & Fremouw, 2008).

In New Zealand, there is evidence of all three types of aggression, and the relationship with drug use is clear. The increasing trend over the last decade or so, especially in regards to the use of amphetamines, which includes MA, is also evidenced. Crime relating to substance abuse was the fourth highest major offence in 2003. For the year ending 30th June 2007, this had risen to be the second largest major offence, behind dishonesty (New Zealand Department of Corrections, 2003). Drugs and anti-social crime accounted for 13.3% of recorded crime in 2007 (Police National Headquarters, 2007), and has risen to account for 15.2% in 2009 (Police National Headquarters, 2009). In relation to offenders themselves, a study of psychiatric morbidity in New Zealand prisons showed that 46.2% of females met criteria for abuse or dependence of a substance (other than alcohol or cannabis), 38.4 % remand males met criteria, and 36.9% sentenced males met criteria (Simpson, Brinded, Laidlaw, Fairley & Malcolm, 1999). This emphasises the point that although aggression and violence is associated with substance use, many other factors play a role in determining who will actually be affected by this relationship.

Although the relationship between substance abuse and aggression is complex, a better understanding of this complexity will develop from research that investigates all the different aspects of the link. By examining whether a single dose of a drug may cause aggression, this study will endeavour to deepen the understanding of this complex relationship.

1.5 Stimulants

Because of the aforementioned relevance of MA and BZP to New Zealand, it is the stimulant class of drug that is of importance in this study, especially the amphetamines which includes MA. Stimulants are the class of drug with the most idiosyncratic literature regarding their relationship to violence, with mass media playing an important role in making people believe that they undeniably generate aggression. Yet the experimental literature is inconsistent, and there is agreement to acknowledge other reasons for the link between stimulants and aggression (Hoaken & Stewart, 2003). Hoaken and Stewart (2003) state that one pertinent aspect is the fact that people who tend to use stimulants may be more likely to be aggressive and also have antisocial personalities, which could imply that they enjoy the stimulation that these substances provide. Anderson (2005) adds that the effects of different stimulants at different developmental periods can have unique short and long term effects. This supports the importance of understanding how drugs affect adolescents.

A substance belonging to the stimulant category, also known as a 'psycho-stimulant', tends to increase behavioural activity. Examples of this increased behavioural activity are elevation of mood, increases in motor activity, alertness, and the brain's metabolic and neuronal activity. Stimulants have been shown to directly stimulate the nucleus accumbens (NA), which is associated with the pleasure pathway, behavioural reinforcement, and the compulsive abuse and dependency of these substances (Anderson, 2005; Couppis, & Kennedy, 2008; Julien, 2001; Spear, 2007b).

Amphetamines are a structurally defined group of drugs belonging to this stimulant group of substances that affect both the central nervous system (CNS) and the autonomic nervous system (ANS). The CNS is affected by the aforementioned release of DA from pre-synaptic storage sites in nerve terminals. Hence, the drug is a potent DA agonist, and also inhibits reuptake of DA (Anderson, 2005; Baumann, Clark, Budzynski, Partilla, Blough, &

Rothman, 2005; Boles & Miotto, 2003; Carlson, 2004; Julien, 2001). Studies also show that stimulation of the DA receptors in the mesolimbic system (which includes the NA) causes behavioural stimulation and increased psychomotor activity. The high dose stereotypical behaviour appears to involve DA neurons in the caudate nucleus and putamen of the basal ganglia (Julien, 2001: Carlson, 2004). There is agreement that the actions leading to increases in aggressive behaviour are complex, and the harmful effects seen in high-dose users include psychosis and other abnormal mental conditions (Brems & Johnson, 2001; Wilkens, Sweetsur & Casswell, 2006). These users show deterioration in social, personal and occupational characteristics, and often experience paranoid ideation. This psychosis is especially evidenced with MA.

Amphetamines are also prone to compulsive abuse. Cocaine and amphetamines are believed to initially cause excess transmitter followed by a state of depletion which is presumed to be associated with changes in mood that may predispose aggression. In addition, withdrawal from these drugs produces a set of characteristic physical and psychiatric effects, and it is the pursuit to alleviate these effects with drugs that can also develop into aggressive behaviour (Boles & Miotto, 2003).

Physical dependence on amphetamines is readily induced in both humans and animals, and follows a classical positive conditioning model. That is, the positive reward received through the pleasurable high, leads to further use and abuse. Tolerance for amphetamines develops rapidly and often results in a need for higher doses. This can result in a vicious cycle of use and withdrawal, involving a need to acquire the drug and sustain a habit. The tolerance combined with the memory of the high leads to further intake, social withdrawal and a focus on procuring drug (Julien, 2001). This demonstrates a combination of all three of Goldstein's ways that propose how substance abuse can be related to aggression.

The findings of the research on chronic or acute use of these stimulants producing aggression are mixed, with most of the research stating that it is chronic use of these stimulants that produces the more aversive effects including aggression (Boles & Miotto, 2003), whilst stating that substance induced aggression during intoxication/use can occur in dependent or nondependent users. Boles and Miotto (2003) report that the significant consequence of chronic use is development of behavioural pathology including paranoid psychosis, impaired reality testing and hallucinations, and that this psychosis has been described as transient, prolonged or persistent. They also report that amphetamine use produces irritability, physical aggression, hyperawareness, hyper vigilance and psychomotor agitation, whereas chronic intoxication can produce a psychotic, paranoid state, including frightening delusions. Increased dosage was found to be associated with delirium involving confusion, fear and anxiety, delusions, paranoid thinking and compulsive behaviour. Boles and Miotto (2003) conclude that amongst the most important effects of amphetamines are mood altering properties which can occur with both acute and chronic administration, and that psychosis induced more by amphetamines than cocaine or other stimulants maybe because of longer duration of action (longer half-life). Chronic use of amphetamines is associated with violence more than any other psychoactive substance.

Forensic and clinical literature clearly demonstrates an association between cocaine abuse and aggression, or acts of violence that arise from the direct pharmacological effects of cocaine for both causal and chronic users (Boles & Miotto, 2003; Davis, 1996; Friedman, 1998; Higgins & Katz, 1998; Long, Wilson, Sufka, & Davis, 1996). On closer examination the results are mixed with inconsistent results, and different results for chronic and acute use. There is agreement that it is not a simple direct pharmacological effect, but a possibly interplay of all different aspects (Hoaken & Stewart, 2003) possibly including all of the aforementioned ways substance can affect violent or aggressive behaviour. Another problem

with the research examining the relationship between illicit drugs and aggression is that all the different substances are often combined. To gain a better understanding of how each substance may be related to aggression, it would be better to examine each substance separately (Boles & Miotto, 2003).

1.6 Methamphetamine (MA)

1.6.1 General

Methamphetamine use has increased significantly over the last decade, fast becoming a world wide problem that is now recognised by the public, the criminal system and researchers (Butler, Wheeler, & Sheridan, 2009; Darke, Kaye, McKetin & Duflou, 2008; Homer et al., 2008; Maxwell, 2005; McKetin et al., 2006; Richards, Bretz, Johnson, & Turnipseed, Brofeldt, & Derlet, 1999; Tyner & Fremouw, 2008; Wu, Pilowsky, Schlenger, & Galvin, 2007). In the adolescent age group, MA is now the second most used drug after marijuana in over 36 countries, and this age group is now identified as the key group at risk of MA use (New Zealand Police, 2009; Wu et al., 2007). The extent of the problem, and the severe consequences of the use and abuse of MA, is so great that it is now referred to as the *Meth Menace* (Tyner & Fremouw, 2008).

Methamphetamine, as with amphetamine, is highly addictive and often abused. Exposure early in life has lasting effects on cognitive processes (McFadden, & Matuszewich, 2007; Rothman & Baumann, 2003; Volkow, Chang, Wang, Fowler, Leonido-Yee, Franceschi, et al., 2001). This is compounded by the ease with which it can be synthesised from general household products like drain cleaner, and ephedrine and pseudoephedrine, which can be found in common cold and ‘flu remedies (McFadden, & Matuszewich, 2007; New Zealand Police 2009; Tyner & Fremouw, 2008; Volkow et al., 2001; Wilkins et al., 2009).

1.6.2 Biology/ Neurotransmitters

Methamphetamine has a chemical structure similar to amphetamine, but with a methyl group in the terminal amino group (Grimes et al., 2006). MA affects the CNS more potently because it is a cationic lipophilic molecule affecting both the sympathetic nervous system (SNS) and CNS, and hence is more potent than amphetamine because of its lipophilic nature which allows greater penetration of the CNS (Homer et al., 2008; Julien, 2001; McKetin et al., 2006; Tyner & Fremouw, 2008).

Compared with cocaine, which is acknowledged as being associated with aggression and violence, *Ice* (which is a 90-100% pure form of methamphetamine) is very similar to crack cocaine. The effects of *Ice* closely resemble and are frequently indistinguishable from cocaine. The main difference is that *Ice* has an extremely long half-life of up to about 12 hours. This results in an intense, persistent drug action, as well as building tolerance much quicker, meaning the user requires more and more of the drug to get the same effect (Cartier, Farabee, & Prendergast, 2006; Julien, 2001; Wu et al., 2007). This can in turn lead to aggression and violence through all three aforementioned ways through more intense biological effects combined with a greater need to acquire more of the drug at a greater cost financially. It is also agreed that these repeated high doses are associated with violent behaviour and paranoid psychosis (Julien, 2001; Maxwell, 2005). Julien (2001) goes on to say that these high doses cause long-lasting decreases in 5-HT and DA in the brain, because the toxic effect targets the neurons that manufacture both of these neurotransmitters (Boles & Miotto, 2003; Homer et al., 2008; McKetin et al., 2006; Sekine, Ouchi, Takei, Yoshikawa, Nakamura, Futatsubashi, et al., 2006). Many researchers agree that studies have indicated that chronic use decreases DA in the NA (Carlson, 2004; Couppis & Kennedy, 2008; Payer, Lieberman, Monterosso, Xu, Fong, & London, 2008; Sokolov & Cadet, 2006). This decrease in DA in the NA can result in unpleasant feelings if the drug is stopped, thus leading to

dependence though negative reinforcement as the user ties to alleviate the unpleasant feelings by taking more of the drug. Julien (2001) also says that *Ice* produces patterns of delusional and psychotic behaviour, but unlike cocaine, this psychosis can persist for several weeks. McKetin et al. (2006) state that, for there to be a causal relationship between MA and aggression, there needs to be a plausible biological pathway through which MA use causes violence. The recognised dysfunctioning of neurotransmitters would support this pathway. But as stated previously, it is clear that this is just one aspect of how the two concepts are related, and all the others need to be considered in any conclusion.

1.6.3 Aggression

There is an abundant amount of research reporting a relationship between MA and aggression, especially *affective defence* (Weinshenker & Siegal, 2002). The key role of biology, through changes in neurotransmitters is acknowledged, yet most researchers agree that the relationship is complex and multi dimensional. Many other factors such as co-morbid psychiatric problems and systemic violence like drug trafficking play a role, hence inferring causality is very difficult (Austin, 2004; Baskin-Sommers, & Sommers, 2006; Boles & Miotto 2003; Brecht, O'Brien, von Mayrhauser, & Anglin, 2004 ; Cartier, et al., 2006; Grimes, et al., 2006; Hall, Hando, Darke, & Ross, 1996; Homer, et al., 2008; Maxwell 2005; McKetin et al., 2006; Miura, Fuliki, Shibata, & Ishikawa, 2006; Payer et al., 2008; Sekine et al., 2006; Sheridan, Bennett, Coggan, Wheeler, & McMillan, 2006; Sokolov, et al., 2004; Sokolov & Cadet, 2006; Tyner & Fremouw, 2008). Boles and Miotto (2003) emphasise the fact that MA use contributes to aggression through both the pharmacological effects, such as agitation, paranoia and psychosis, and the systemic violence factors such as drug trafficking. Route of administration has also been shown to make a difference with injection being related to significantly more aggressive behaviour (Hall et al., 1996). Disorganised cognitions,

involving paranoia and psychosis are usually related to persecutory delusions and perceived threat, and are the commonly associated psychiatric problems associated with chronic use of MA and resulting aggression (Baskin-Sommers, & Sommers, 2006; Maxwell, 2005; McKetin et al., 2006; Wilkins et al., 2009). This results from the misinterpretation of others' intentions, and perceived threat which can instigate a violent reaction (Cartier et al., 2006). Cartier et al's study (2006) also found that those using MA were younger than non-users. In addition, the authors controlled for drug trade involvement, and still found a significant relationship between MA and aggression. This provided a good argument for a biological cause for the link. Further support comes from Sekine et al's study (2006) which also controlled for other substance abuse and also found an association between aggression and MA. It is clear from the literature that aggression is associated with chronic abuse resulting in paranoia and psychosis where the intentions of others are misinterpreted.

The media play an influential role in portraying the perceived conclusive causal link between MA, aggression and violence (Sheriden et al., 2006; Tyner & Fremouw, 2008). Although there is overwhelming and compelling evidence for the relationship between MA and aggression, the exact nature of this relationship is still poorly understood (Tyner & Fremouw, 2008) and most researchers agree that although biology plays a role, the relationship is too complex to simply imply one cause.

Most of the results of studies supporting this relationship between MA and aggression describe the effects of chronic use of MA and aggression, and involved both human and animal subjects, with less interest in examining acute administration (Austin, 2004; Brecht et al., 2004; Butler et al., 2009; Hall et al., 1996; Homer et al., 2008; Miczek & O'Donnell, 1978; Miura et al., 2006; Richards, et al., 1999; Sekine et al., 2006; Sokolov & Cadet., 2006; Sokolov, et al., 2004; Volkow et al., 2001; Vorhees, Reed, Morford, Fukumura, Wood, Brown, et al., 2005; Wilkins et al., 2009; Zweben, Cohen, Christian, Galloway, Salinardi,

Parent, et al., 2004). The studies that do investigate acute doses are inconsistent in their findings. While Crowley (1972) did find that rats administered MA were more aggressive, it is questionable whether this study was in fact an acute study because the rats were administered MA every three days over a period of weeks. In contrast, other studies using animals did not support aggression resulting from an acute dose of MA when they compared acute with chronic administration (Miczek & O'Donnell, 1978; Richardson, Karczmar & Scudder, 1972; Sokolov, et al., 2004; Sokolov & Cadet, 2006). It is agreed that an acute dose may enhance a person towards acting aggressively if they are provoked, or in association with other conditions (McKetin et al., 2006; Sheriden et al., 2006). This may relate into *affective defence* where aggression is performed due to a perceived threat on territory, or a mate. One argument is that aggression does occur in a dose dependent manner, that is, the higher the dose, the more chance of aggression (Miczek & O'Donnell, 1978; Tyner & Fremouw, 2008).

1.6.4 Crime

Under the Misuse of Drugs Act, 1975, MA has been classified as a Class A, or schedule 1 drug in New Zealand since 2003 (Ministry of Health, 1975). To be classed in this category, which also includes cocaine and heroin, a drug must be deemed to be a very high risk of harm, and is illegal (Ministry of Health, 1975).

When examining New Zealand's association with MA and its resulting influence on aggressive and criminal behaviour, one survey (Wilkins, Rose, Trappitt, Sellman, Adamson, DeZwart, 2004) arrived at the following conclusions: 1) There is an increased number of MA users coming to the attention of Police and drug treatment, 2) Methamphetamine's easier availability has resulted in a greater cross section of society now using it, 3) there is an increase in marketing of MA to lower socio-economic groups, and 4) there is an increase in

violence associated with its use (including serious and domestic violence). These conclusions were derived from information supplied by drug enforcement key informants, and drug treatment key informants. Both groups noticed a significant number of younger people now using MA (33-46 % agreement). Up to 73 % noticed more serious and violent crime being associated with its use, while 85 % noticed a general change in violence associated with its use. Over the last five years statistics from New Zealand have shown a similar trend in the increased use of MA and its relationship to an increase in crime and violence involving aggression. Statistics from 2006 showed that non-cannabis drug offences (including MA) more than doubled from 4 per 10,000 in 1996 to 10 per 10,000 in 2005. After this peak, there is the acknowledged levelling out with statistics from 2009 showing 4 per 10,000. Drug and anti-social offences in 2005 equalled 12.7 % of all recorded offences, and the major contributor to the growing non-cannabis related drug offences was possession of MA/amphetamine, and their utensils for use. The survey also said the New Zealand police had noted a switch in the drug market from cannabis to MA and other drugs (STANZ, 2006). A 2007 study involving people recently apprehended and detained in watch houses that participated in a programme that measured drug and alcohol use, reported that 44 % said they had used MA, and 33.6 % cited it as the worst drug for making them angrier **(**Hales & Manser, 2007).

The most recent statistics support this trend for both MA and the more pure form of crystal MA (*Ice*) and even though the number of clandestine MA laboratories that have been dismantled by Police has risen from five in 1999 to 133 in 2008, evidence suggests a levelling out of MA use, following a consistent increase over the last ten years (New Zealand Police, 2009; Wilkins et al., 2009). Data from the New Zealand Police Illicit Drug Strategy to 2010 show that illicit drugs, including MA now cost New Zealand up to 1.31 billion per year through aspects such as Police time and hospitalisations. MA users that were part of this

study reported spending more money on MA than any other drug, and that they were more likely to pay for this with criminal activity, as well as being more likely to access mental health services as a result of their use (New Zealand Police 2009; Wilkins, et al., 2009). One key consequence of this increased expenditure was the fact that money spent on drugs is not available for food, housing, or education, and is therefore a drug related harm. In 2005, MA and *Ice* were considered extremely risky to purchase compared with other substances (Wilkens, et al., 2005).

Findings from the Illicit Drug Monitoring System (IDMS) support this issue of increasing cost, and criminal activity resulting from it, by reporting that the price of MA has risen from 2006, causing more problems paying for it. This study reported that the median price of a gram of MA is now $700 compared to $610 in 2006, and that a median spendature on a single occasion is now $200 (Wilkins et al., 2009). The same study reported that 48% of users interviewed said it was now easier to obtain MA, with 62% saying they had purchased it from a drug dealer, and 42% from a gang member or associate. This would provide evidence for both *systemic* and *economic compulsive* violence and aggression to occur along side psychopharmacological aggression. Further evidence for the association of MA use with aggression and crime is that those users spending more than $1000 per month, committed 2367 more property crime than others who did not buy MA (Wilkins, et al., 2009).

In regards to adolescent or youth using MA and committing crime, findings from the IDMS show that 13 was the mean age for Users of MA associated with truancy from school, and 45% of users had been suspended from school, with the main reason of suspension being fighting for 40%. Youth also cited MA use as being highly associated with expulsion from school, committing property crime and selling of drugs as ways to make money and pay for their habits. In relation to violent crime, 42% had committed a violent crime, and the mean age for their first offence was just 17 years of age. Six percent of these youth had committed

a violent crime in the past month, with a mean age of 17 as age of first violent offence. This study also showed that there was increased Police contact through both anti-social behaviour and criminal activity to pay for the drugs, and in the past 12 months, 18% had been arrested for a violent crime (Wilkins, et al., 2009).

1.7 1-Benzylpiperazine (BZP)

Originally synthesised for use as an anti-parasitic agent to treat infestations of large roundworms and pinworms (Gee & Fountain, 2007), 1-benzylpiperazine (BZP) is a piperazine derivative which comes as either a hydrochloride salt or a free base. Unlike countries such as the USA, Japan and Australia, it was not until 18th July 2008 that New Zealand followed suit and passed legislation which placed BZP into Class C of the New Zealand Misuse of Drugs Act 1975, making the selling of it illegal. Research since that time has shown that the prohibition of BZP has had a negative impact on both its use and availability, with it now being more difficult to obtain and having a higher purchase price in 2008 compared with 2007 (Wilkins et al., 2009).

Because of the known risks associated with the use of MA, people sought a safer alternative, and BZP is often perceived as a safer option (Aitchison & Hughes 2006; Baumann et al., 2005; Brennan, Johnstone, Fitzmaurice, Lea, & Schenk, 2007). Recreational drug users as well as people such as truck drivers who wish to stay awake longer and have increased energy, are likely to use BZP as a safer alternative to MA (Gee, Richardson, Woltersdorf, & Moore, 2005; Johnstone, Lea, Brennan, Schenk, Kennedy, Fitzmaurice, 2007). Research on BZP has shown that the psychotropic effects on behaviour and neurochemistry may be indistinguishable from amphetamines (Aitchison & Hughes, 2006; Alansari & Hamilton, 2006; Baumann, et al., 2005; Brennan, et al., 2007; Herbert & Hughes, 2009). Both substances share stimulant properties that produce the euphoric effects associated

with recreational drugs of abuse, and both affect DA and 5-HT levels in the CNS (Baumann, et al., 2005: Fantegrossi, Winger, Woods, Woolverton, & Coop, 2005; Gee et al., 2005; Gee & Fountain, 2007; Herbert & Hughes, 2006; Johnstone et al., 2007). Fantegrossi's (2005) study involving rhesus monkeys, also supports the likelihood of BZP being addictive in a similar fashion to MA and cocaine through the fact rhesus monkeys self-administered BZP at a similar rate to cocaine. Johnstone et al. (2007) state that an increase in dopaminergic neurotransmission underlies much of the behaviour exhibited by rats that have been administered BZP. They also state that the effects were similar to those seen after MA administration (Gee et al., 2005). This study showed patients admitted to hospital developed some adverse reactions up to 24 hours after ingestion of BZP, and concluded that there is a narrow safety margin for some users due to aspects such as intrinsic pharmacodynamic properties. They also reported that since 2004 when BZP became better known and accessible, emergency departments noticed a rapid increase in patients who presented with BZP toxicity, which included heart palpitations, agitation, nausea and vomiting. Gee et al. (2005) also state that there have been numerous reports of BZP causing either a toxic paranoid psychosis or exacerbating an existing mental illness. As does much of the research on BZP, this study made no mention of examining acute doses in comparison to chronic use. Most cases in this study used varying amounts of BZP and it was not stipulated whether they were chronic users. It was concluded that most patients took multiple doses because the first dose did not produce desired effects immediately, implying the possibility of increased doses and abuse potential.

Because the research on BZP is limited, especially in relation to the effects of acute doses which has no empirical data to date (Aitchison & Hughes, 2006), researchers have emphasised the need and importance of further investigations of BZP's acute behavioural effects (especially involving DA) in order to help better understand its functioning (Aitchison

& Hughes, 2006; Baumann et al., 2005; Johnstone et al., 2007). By combining BZP with MA in research may provide a better understanding of the similarities or differences of these two drugs, especially in relation to causing aggressive behaviour.

2.0 Aims and Hypotheses of this Study

The aim of this current study was to examine whether an acute dose of either MA or BZP will result in aggressive behaviour in adolescence. This question has been largely ignored in much of the research to date, with most of the literature concentrating on chronic use resulting in paranoid psychosis and dysfunction in mood through the effects on DA and 5-HT in adults. There appears to be minimal research examining whether a single dose of either drug will invoke the radical behavioural changes that the media is so intent on portraying as fact.

Because of the many ethical and practical considerations of using human subjects in a study such as this, and the complexity and multi dimensional nature of aggressive behaviour, an animal model of aggression was chosen and has support throughout the literature (McEllistrem, 2004; Sokolov & Cadet, 2006; Sokolov et al., 2004). The research states that although it has been a daunting task using animal models to explain pathological aggression, the developmental stage of adolescence is not uniquely human, with similarities across many species including the rat, which show adolescent-typical behavioural patterns. These across-species similarities in behavioural and physiological attributes of adolescence provide acceptable face and construct validity for the use of animal models when studying the potential neurotoxic effects during adolescence (Spear, 2007b). Weinshenker & Siegal (2002) support this view by stating that the neural basis of aggressive behaviour in animals does

indeed parallel those observed in humans. Volkow et al. (2001) believe that because animal studies have shown MA to be neurotoxic, there should be concern over whether this equates to humans.

The mixed results thus far in animal research on aggression and MA can be the result of the different animals and conditions used for each piece of research. Rats are often used, as well as cats and mice. What the researchers do agree upon is that there is promising evidence for this relationship from the use of animal models (Sokolov & Cadet, 2006).

Because of the inconsistencies in the research and the neglect of a single acute dose of either drug, this study investigated whether or not aggression will result from an acute dose of either MA or BZP in adolescence.

3.0 Method

3.1 Subjects

The subjects were 90 male and 60 female PVG/C hooded rats aged 41 to 50 postnatal days (PND), bred in the Animal Facility of the Department of Psychology, University of Canterbury. The average weight of the pups during testing was 131.7 grams, with the lightest pup weighing 104 grams and the heaviest being 170 grams. When 30 days old, all pups were weaned and housed in 525 x 330 x 230mm plastic cages. Sixty of the male pups were housed with a female pup, whilst the remaining 30 male pups were housed with up to four pups. The focal male rat was housed with a female in an effort to increase the rat's perception of its own territory that it would need to defend against when intruded upon (Malkesman, Maayan, Weizman, & Weller, 2006; Weinshenker & Siegal, 2002). In addition, the cage would have a female scent in it when the intruder rat was introduced, again possibly increasing the chance of aggressive responses occurring through *sex-related* aggression where sexual arousal can increase levels of hostility (Weinshenker & Siegal, 2002). Subjects were housed in a controlled environment, with a constant temperature of 20± 1 ºC, a 12 hour light/dark cycle (lights came on at 8am), and ad libitum food and water. All subjects were treated in accordance with the guidelines set by the Australian and New Zealand Council for the Care of Animals in Research and Teaching, and the Animal Ethics Committee of the University of Canterbury approved all procedures (see Appendix A).

3.2 Apparatus

This study utilized the empirically supported resident/intruder test of aggression. This test has been cited as a good measure of *affective defence,* or *territorial* aggression that provides a classical demonstration of motivation to be aggressive that results from the

perceived threat from another organism, as well as the perception of having to protect its own territory (Weinshenker & Siegal, 2002), and used successively by many previous researchers (Johns & Noonan, 1995; Miczek, & O'Donnell, 1978; Sgoifo, De Boer, Haller & Koolhas, 1996; Sokolov, & Cadet, 2006). It involves recording behaviour in the subject's home cage, which in the present study measured 525 x 330 x 230mm. Since its occupation following weaning, the floor of the cage had been covered with absorbent wooden pellets. For all experimental observations, the cage sat on a 700mm high table under a video camera mounted in a wooden arm 800mm above the cage. The experimental room was evenly illuminated by dim, overhead fluorescent lighting.

3.3 Drugs and Rationale for Doses

3.3.1 Methamphetamine

MA was donated as a pure crystal form of the drug by Environmental Science & Research Limited (ESR, Wellington, New Zealand). The MA was crushed and then dissolved in 0.9% saline to provide High and Low doses of 1 and 2 mg/kg respectively. Previous research states that the lowest dose of MA capable of invoking release of dopamine (DA) and serotonin (5-HT), which is required to illicit aggressive responses, is 1mg/kg (Baumann et al., 2005; Brennan et al., 2007; Hughes & Grieg, 1976). Because of this, this study used this dose as its minimum dosage, and 2mg/kg as a comparison dosage.

3.3.2 1-Benzylpiperazine

BZP was purchased from ABRC Gmbh & Co, Karlesruhe, Germany. This was diluted in 0.9% saline to provide High and Low doses of 10mg/kg and 20mg/kg respectively. Because MA is reported to be ten times stronger than BZP, these doses were adopted to

achieve similar levels of potency to 1 and 2 mg/kg MA, as has typified previous research (Campbell, Cline, Evans, Lloyd, & Peck, 1973; Gee, et al., 2005; Herbert & Hughes, 2009; Johnstone et al., 2007; Wilkins et al., 2009).

3.4 General Procedure

On Post Natal Days (PND) 41-50, 60 male rats were randomly assigned to five experimental groups that were injected with saline (control), 10.0 mg/kg or 20.0 mg/kg BZP, or 1.0 mg/kg or 2.0 mg/kg of MA. This periadolescent age is equivalent to adolescence in humans (Smith, 2003; Spear, 2007a), when the brain is in a state of transition, both anatomically, and neurochemically. This is especially so for the prefrontal and limbic areas and systems operated by DA and 5-HT (Aitchison & Hughes, 2006: Vorhees et al., 2005). Drug use during this age has been shown to result in long-term changes to the developing brain. The brain of an adolescent may respond differently than at other ages to the influence of a substance, and it is during this age that drug use often begins (Vorhees et al., 2005).

One hour before testing, the female was removed from the cage, along with food and water. This was done in an attempt to increase the irritability, anxiety or emotionality of the resident rat, and thus increase the possibility of aggression as a reaction to this elevated anxiety or emotionality. This would incorporate the aforementioned *irritable* type of aggression (Weinshenker & Siegal, 2002). Twenty minutes prior to testing each rat was interperitoneally injected with the appropriate drug or saline. Following this delay, an intruder rat was placed in the cage with the resident rat for exactly ten minutes.

Aggressiveness was recorded by noting the occurrence of certain responses on a prepared data sheet (Appendix B). The main measure of aggression was the 'latency time to attack' (LTA) the intruder by the resident rat, and was defined as the "*first instance (measured in seconds) of movement by the focal/resident rat towards the stimulus/intruder*

rat at a distance greater than the length of a rat, resulting in near or actual contact", and involved 'Aggressive Posture', defined as *"the focal rat restraining the intruder rat with their front paws, either holding down the other rat or up on hind legs "boxing" with other rat"*.

When it became apparent that neither of these responses were the first instance of contact, another measure of 'General/Non-Aggressive Contact' was utilised. If either of the previous two responses occurred following this initial contact then they were recorded as a "frequency of occurrence" response, not as a LTA. 'General/Non-Aggressive Contact' was defined as simply the first move resulting in near contact or contact not involving the aforementioned responses. This was measured manually with a stopwatch by the observer in seconds because in most instances this was the first contact made by the resident rat. This measure was included to determine if the drug had any effect on the resident rat's speed of approaching the intruder which could have been dependent on aggressiveness or confrontation-related anxiety.

Also recorded were the frequencies of the following responses associated with aggression (Johns & Noonan, 1995; Malkesman et al., 2006; Weinshenker & Siegal, 2002).

- Chase – any pursuit of the stimulus/intruder rat around the cage by the focal/resident rat. Occurrence of the behaviour stops as soon as the focal rat stops moving, or contact is made (does not include first contact as mentioned above). The resident rat must chase the intruder rat over a distance equivalent to the length of a rat and must include the intruder rat *moving away* from the resident rat.

- Sniffing - any aggressive sniffing by the resident rat of the anal/genital region (this may/may not include use of paws) of the intruder rat. The behaviour is deemed to have stopped when the sniffing stops for 1 second.

- Alert position - the resident rat exhibits a sudden interruption of all movement with its head directed towards the intruder rat. It must be perfectly still for at least 1 second duration, and must be facing the intruder rat, not upwards or to the side.
- Self-groom - the resident rat grooms itself by licking body fur and/or face washing (most often after a fight attack). The response is regarded as having ceased whenever the grooming stops for more than 1 second.
- Avoidance - any move greater than the length of a rat that the resident rat makes to escape or distance itself from the intruder rat. The response is regarded as having ceased when movement stops for more than 1 second.
- Standing on Hind legs - any instance when the resident rat stands up on its hind legs and faces the intruder rat. This does not include standing up to look out of the top of the cage. It DOES NOT include contact with the intruder.

3.5 Statistical Analyses

All raw data was analysed with one-way analysis of variance (ANOVAs) using the Statview statistical programme and presented in graphical form as means ± S.E.Ms (see Figures 1-8). For each aggressive behaviour, a one-way ANOVA was performed for each drug separately to determine the effects of the two dose levels in comparison with the saline condition. Because equivalent potency of the two drugs at each dose level could not be ensured, they were each separately compared with the common saline group (in accord with previous practice, Herbert & Hughes, 2009). When a significant dose effect occurred, post hoc comparisons were made by means of Scheffe tests.

4.0 Results

4.1 Aggressive Posture

As shown in Figure 1 below, control rats (administered saline solution) restrained the intruder rat with their front paws, by either holding down the other rat or up on hind legs, boxing, significantly more often than rats administered each dose of both MA, $F(2,33) = 10.44$, $p<.001$, and BZP, $F(2,33) = 9.48$, $p<.001$. There was no significant difference between the two dose levels for either drug.

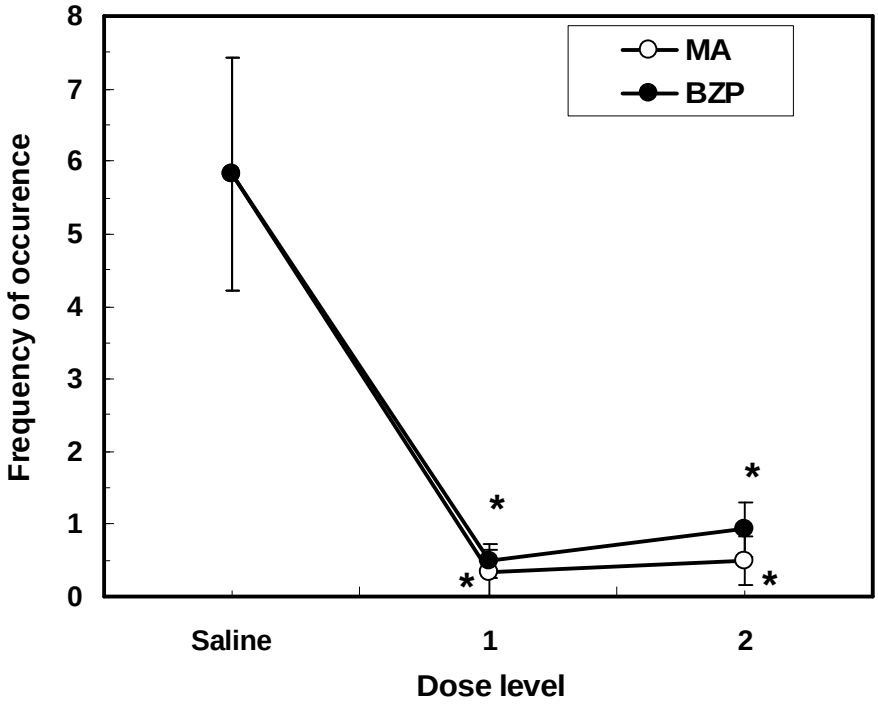

Figure 1. **Means ± S.E.Ms aggressive posture scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group.**

4.2 General/Non-Aggressive Contact

For both MA and BZP, even though both doses produced shorter latencies to approach the intruder rat, the difference was not significant for either drug in comparison to the saline group, MA, $F(2,33) = 2.25$, $p = .1338$, BZP, $F(2,33) = 2.14$, $p = .1212$ (see Figure 2 below). This was most likely due to the high variability of the control group as shown by its large SEM (± 55.18).

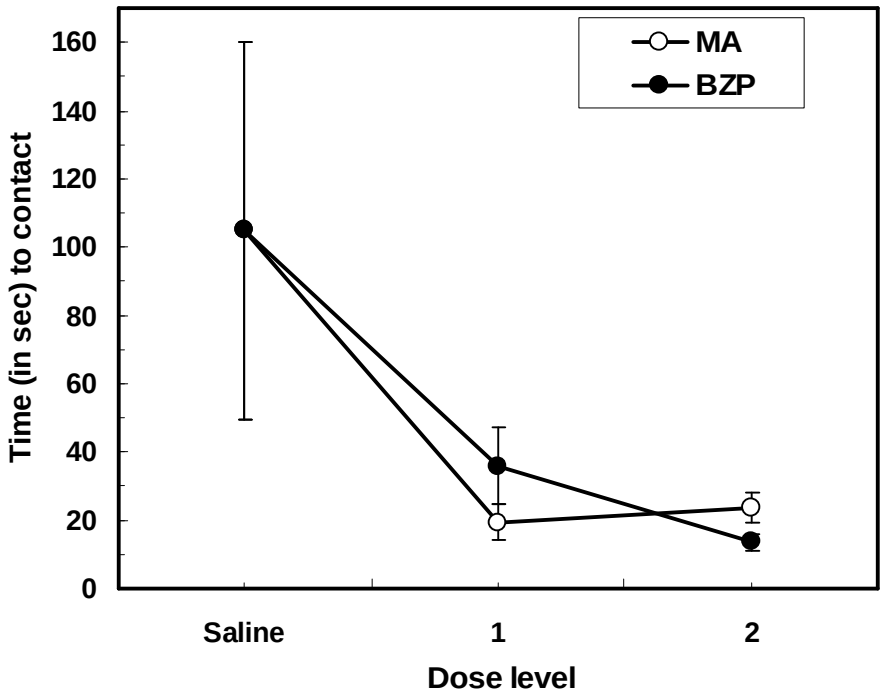

Figure 2. **Means ± S.E.Ms general/non-aggressive contact scores measured as a latency time to attack in seconds following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose).**

4.3 Chase

Rats administered saline chased the intruder rat significantly more often than rats administered either MA, $F(2,33) = 7.52$, $p<.01$, or BZP, $F(2,33) = 8.36$, $p<.01$. There were no significant differences between the two doses for either drug (see Figure 3 below).

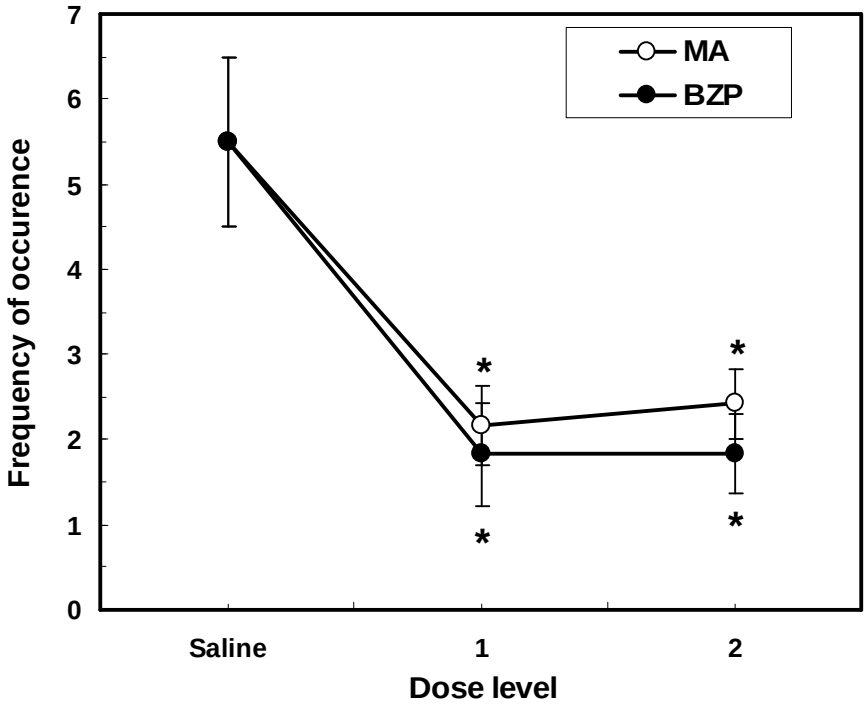

Figure 3. **Means ± S.E.Ms chase scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group.**

4.4 Sniffing

Rats administered saline sniffed the intruder rat significantly more often than those administered either MA, $F(2,33) = 14.99$, $p<.001$, or BZP, $F(2,33) = 12.31$, $p<.001$. For rats administered MA there was no difference between doses for the frequency of sniffing.

However, for rats treated with BZP, the higher dose resulted in significantly more sniffing of the intruder rat by the resident rat (see Figure 4 below).

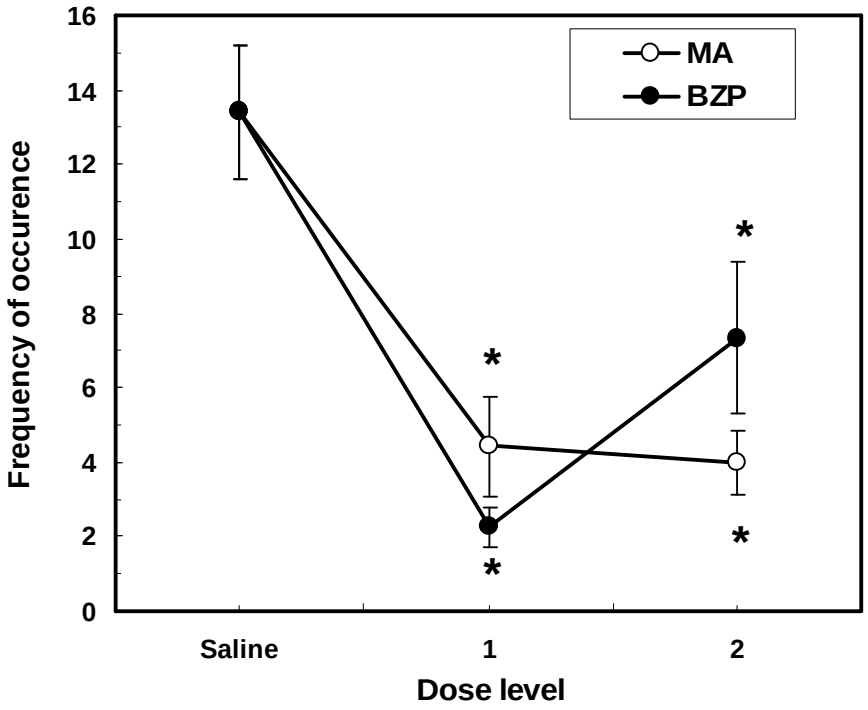

Figure 4. **Means ± S.E.Ms sniffing scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group.**

4.5 Alert Position

Rats treated with MA were marginally significantly affected in adoption of the Alert Position, $F(2,33) = 3.16$, $p = .055$. This arose from a significant difference between the saline and the Low dose, but not the High dose group. Adoption of the Alert Position was significantly affected by BZP, $F(2,33) = 6.20$, $p < .01$, and interestingly, similar to MA, only

the Low dose resulted in a significantly higher frequency of the response. The difference between the low and the high dose of BZP was significant (see Figure 5 below).

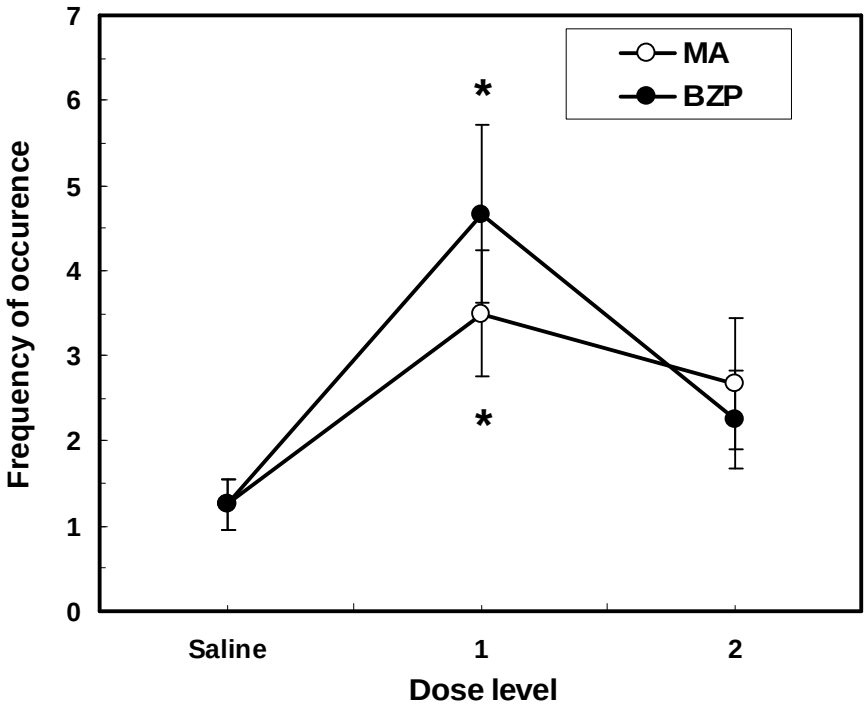

Figure 5. **Means ± S.E.Ms alert position scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group.**

4.6 Self-Grooming

Rats treated with both MA and BZP displayed significantly less self-grooming than those treated with saline, MA, $F(2,33) = 5.16$, $p<.05$, BZP, $F(2,33) = 4.11$, $p<.05$. Differences between the two dose levels were not significant for either drug (see Figure 6 below).

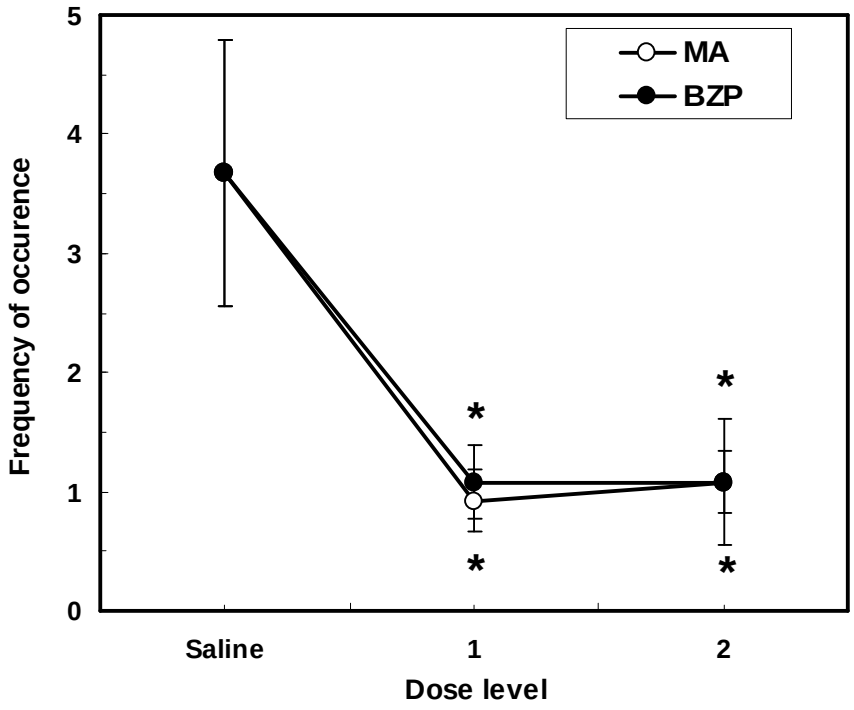

Figure 6. **Means ± S.E.Ms self-grooming scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group**

4.7 Avoidance

Rats treated with MA avoided the intruder rat significantly more often than rats in the saline group, $F(2,33) = 5.05$, $p<.05$. There was no significant difference between the two doses. No significant effect occurred for rats treated with BZP, $F(2.33) = .04$, $p = .9649$ (see Figure 7 below). Differences between MA- and BZP- treated rats were significant for both dose levels of each drug i.e., level 1, $t(22) = 4.31$, $p > .001$; level 2, $t(22) = 2.57$. $p < .05$

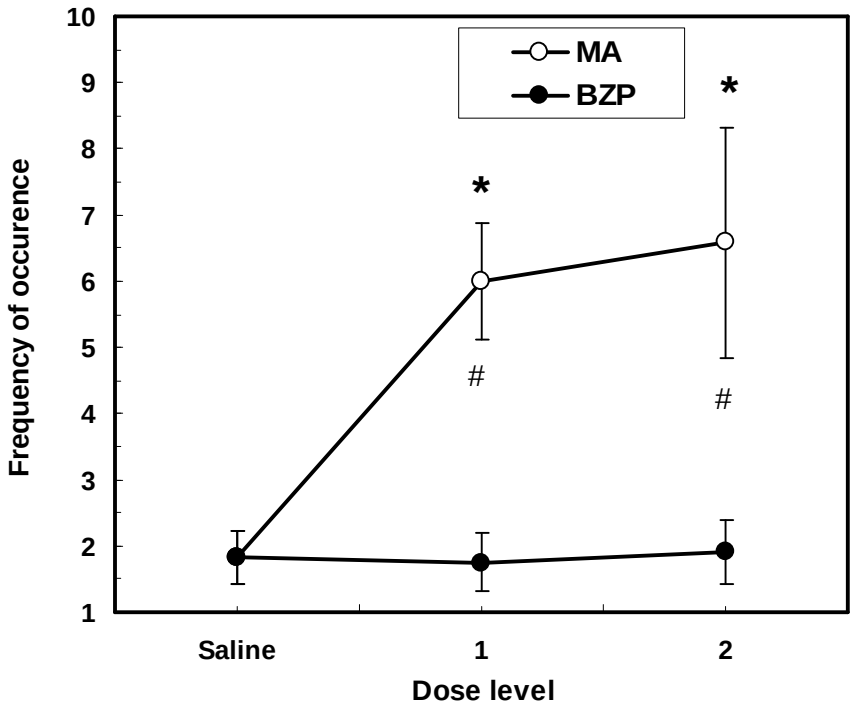

Figure 7. **Means ± S.E.Ms avoidance scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group. # Significantly different from the other drug group for the same dose level.**

4.8 Up on Hind Legs

Rats administered MA reared up on their hind legs significantly more often than those administered saline, $F(2,33) = 6.67$, $p<.01$. There was no significant difference between the two doses. There was also a significant effect of BZP on this response, $F(2,33) = 3.55$, $p<.05$, but only the 'Low' dose produced a significantly higher frequency than that shown by saline-treated rats. Rats treated with 2 mg/kg MA displayed this response significantly more often than rats treated with 20 mg/kg BZP, $t(22) = 2.23$. $p < .05$, but there was no significant

difference between the two drugs at the lower dose level, $t(22) = 1.33$, $p > .1$ (see Figure 8 below).

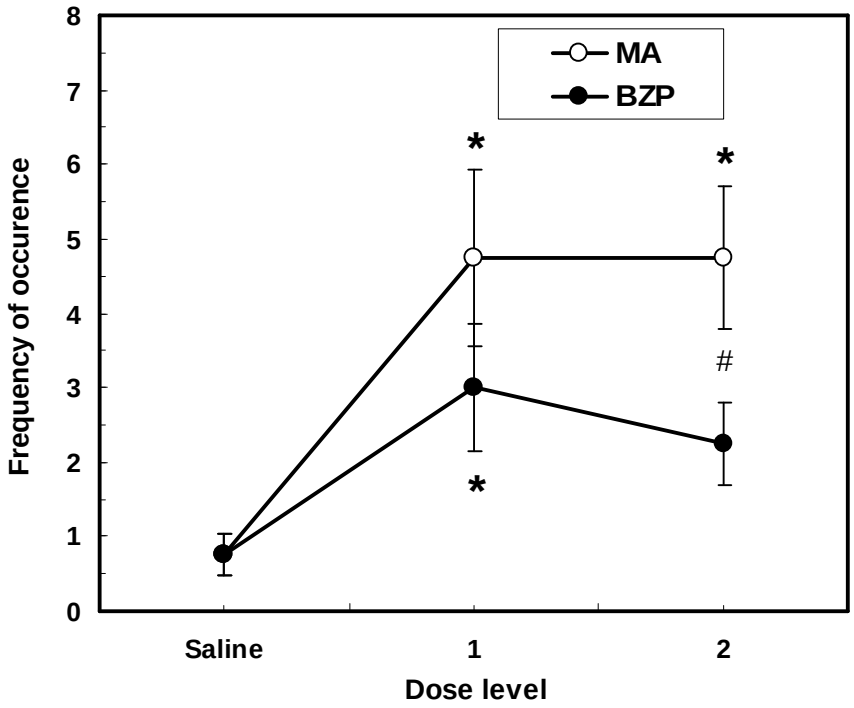

Figure 8. **Means ± S.E.Ms up on hind legs scores following treatment with saline (n=12), 10mg/kg 1-benzylpiperazine (BZP, n=12, low dose) or 1mg/kg methamphetamine (MA, n=12, low dose), or 20mg/kg1-benzylpiperazine (BZP, n=12, high dose) or 2mg/kg methamphetamine (MA, n=12, high dose). * Significantly different from the saline group. # Significantly different from the other drug group for the same dose level.**

For a full display of means and S.E.Ms for all eight behavioural measures, please see Appendix C.

4.9 Comparative Summary of all Drug Effects

Table 1 below provides a summary of all the results described above. From inspection of the table, it is clear that both drugs had similar effects on all measures of aggression,

showing either no significant difference from the saline group, or a decrease in the aggressive behaviour. The exceptions to this were the 'avoidance' and 'alert position' responses which resulted in an increase in both cases in comparison to the saline group in at least one of the doses.

Table 1
Summary of the Behavioural Effects of Methamphetamine and 1-Benzylpiperazine in Comparison to a Saline Group

Measure/Behaviour	Behavioural Effect	
	MA	BZP
Aggressive Posture	Decreased by both doses	Decreased by both doses
General/Non-Aggressive Contact	No effect	No effect
Chase	Decreased by both doses	Decreased by both doses
Sniffing	Decreased by both doses	Decreased by both doses
Alert Position	Increased by lower dose	Increased by lower dose
Self-Grooming	Decreased by both doses	Decreased by both doses
Avoidance	Increased by both doses	No effect
Up on Hind Legs	Increased by both doses	Increased by Lower dose

5.0 Discussion

The popular media portrays MA as a drug that will cause addiction with a single dose, and adverse effects will follow, such as aggressive behaviour. Research on MA and BZP provides little evidence for this. The aim of this study was to examine if an acute dose of either MA or BZP would result in increased aggression. This study randomly assigned 60 adolescent rats, aged between post natal days (PND) 41 to 50 to either a saline group, or a Low (1mg/kg MA or 10mg/kg BZP) and High (2mg/kg MA or 20mg/kg BZP) dose group. Each rat was then exposed to the well-established resident/intruder test of aggression (Johns & Noonan, 1995; Miczek, & O'Donnell, 1978; Sgoifo et al., 1996; Sokolov, & Cadet, 2006; Weinshenker & Siegal, 2002). Aggression was assessed by means of eight previously used behavioural measures (Aggressive Posture, General/Non-Aggressive Contact, Chase, Sniffing, Alert Position, Self-Groom, Avoidance, and Standing on Hind legs).

5.1 Summary of Results

Overall, the results showed that rats administered either MA or BZP, at both low and high doses, displayed less aggressive behaviour than control rats administered saline. The exceptions to this were for measures involving anxiety or fear, or psychomotor agitation, which have been shown to be increased by MA and BZP in previous research (Cancela, et al., 2001; He, et al., 2005; Herbert & Hughes, 2009). These anxiety-related behaviours may be associated with aggressive tendencies, through factors such as heightened states of arousal, increased energy and the tendency to perform risky behaviours (Boles and Miotto, 2003; Cancela et al., 2001; He et al., 2005; London et al., 2004). The overall non-aggressiveness of the drug-treated rats was also supported by the fact that the initial main aggressive behaviour measures of Latency Time to Attack, and Attack Posture were not actually the first instances of contact as observed in other research using this test of aggression (Johns & Noonan, 1995;

Miczek, & O'Donnell, 1978; Sgoifo et al., 1996; Sokolov, & Cadet, 2006). Because of this, another latency time measure was implemented. This was the General/Non-Aggressive Contact measure, which was actually a latency to approach measure instead of an actual aggressive attack. This measure was included to determine if the drug had any effect on the resident rat's speed of approaching the intruder which could have been dependent on either aggressiveness or confrontation-related anxiety.

5.1.1 Aggressive Posture

Results from this behavioural measure indicated that an acute dose of either MA or BZP did not increase aggressive behaviour. Control rats administered saline restrained the intruder rat with their front paws, by either holding it down or by up on hind legs boxing with it, significantly more often than rats administered either MA or BZP. This significant difference was consistent for both high and low doses of each drug. For both drugs there was no significant difference in aggression between dose levels meaning it made little difference whether the rat was administered the low or high dose of either drug. When compared with the control group, both doses of the two drugs showed very similar patterns of effects across comparative doses (high versus high, and low versus low, as illustrated by their graphical representations).

This lack of aggression displayed by rats administered either MA or BZP compared to saline treated rats may be a result of the immediate intoxication effects associated with these substances, namely, the novelty of the experience because of no previous exposure to the drugs. These effects include a euphoric high and pleasure experienced by the rats from their first exposure to these stimulant drugs (Boles & Miotto, 2003; Carlson, 2004; Julien, 2001), and are components of Hoaken and Stewart's (2003) pharmacological effects of intoxication. This would be in comparison to the aggressive behaviours resulting from the adverse and

unpleasant emotions resulting from psychosis and paranoia associated with chronic use, and the acknowledged changes in monoamine functioning. This would provide support for the view that it is only chronic use that causes aggression through changes in monoamine functioning (Boles & Miotto, 2003; Homer et al., 2008; McKetin et al., 2006; Sekine et al., 2006).

5.1.2 General/Non-Aggressive Contact

Although there was no significant effect for either drug in comparison to the control group, from casual inspection of Figure 2, rats administered both doses of either MA or BZP may have appeared to approach the intruder rat more quickly than control rats. Although the non-significant outcome could have resulted from the high variability amongst saline-treated rats (SEM = 55.18 versus 5.30 and 4.48, and 11.14 and 2.57 for each dose of MA and BZP respectively), repeating the ANOVAs after removing two outlying control rats with extremely long approach latencies (401 and 602 seconds) still did not result in a significant effect for either drug i.e., saline = 25.63 ± 6.87, low dose MA = 19.46 ± 5.30, high dose MA = 23.73 ± 4.48 (F2,31 = 0.33, p = .723), low dose BZP = 36.03 ± 11.14, high dose BZP = 13.65 ± 2.57 (F2,31 = 2.17, p = .1312). It is therefore abundantly clear that neither drug affected this measure.

5.1.3 Chase

Treatment with each dose of MA or BZP reduced the number of times the rats chased each other and hence their aggressiveness. As with the previous two aggression measures there was no significant difference between the two dose levels for either drug.

5.1.4 Sniffing

Both doses of each drug significantly reduced sniffing thereby providing further support for the control rats being more aggressive. Of interest, because BZP is considered a milder drug than MA, the high dose of BZP resulted in the most sniffing for the four doses and was significantly greater than the low dose of BZP. This high dose of BZP was not significantly different from either dose of MA, and was very similar to the 1mg/kg dose of MA. This may provide further evidence for the doses of each drug being comparable, as shown in past research (Campbell et al., 1973; Gee, et al., 2005; Herbert & Hughes, 2009; Johnstone et al., 2007; Wilkins et al., 2009). Contrary to most other responses (except avoidance described below), the two drugs did not follow a similar dose-related trend. This implies that rats treated with a high dose of BZP were more inclined to approach and investigate the intruder rat, showing less anxiety, but not evoking aggression.

5.1.5 Alert Position

For this behaviour there was a significant increase in rats administered a drug in comparison to control animals. Those administered a low dose of both drugs adopted this position significantly more often than control rats. Although this behaviour is regarded as an aggressive response, it may reflect a slight elevation in anxiety rather than aggressiveness. This could be due to the fact anxiety involves the fight or flight response which can include freezing (Craske & Barlow, 2008), and is supported by research reporting an increase in anxiety in rats administered MA and BZP (Aitchison, & Hughes, 2006; Cancela, et al., 2001; He, et al., 2005; Herbert & Hughes, 2009; London et al., 2004). A rat adopting the alert position may involve some fear- or anxiety-related freezing in response to a perceived threat from an intruder. Increased anxiety and the fight or flight response, has been associated with changes in mood and a heightened state of arousal, which at extremes may lead to aggressive

acts (Cancela, Basso, Martijena, Capriles, & Molina, 2001; He, Xu, Yang & Li, 2005; London, Simon, Berman, Mandelkern, Lichtman, Braman, et al., 2004). These aggressive acts might arise from the fight mode of responding being deployed for defence. This possibility would also support one of Hoaken and Stewarts' (2003) four physiological effects used to conceptualise intoxication (alteration of the psychomotor system; alteration of the anxiety and/or threat system; alteration of the pain system; and, alteration of certain higher order cognitive capacities), that are likely to increase the chances of aggression. The effect involved here is through alteration of higher cognitive capacities. In this lower state of arousal these results coincide with other results signifying a reduction in aggression, not the apparent increase.

This increase in alertness for rats treated with either MA or BZP may also relate to the aforementioned intoxication symptomology for these two drugs. One of the acknowledged maladaptive behavioural or psychological changes associated with intoxication from stimulants (which characterised both MA and BZP) is hyper-vigilance (Carlson, 2004). Hyper-vigilance would appear similar to the alert position as both behaviours involve the constant scanning, or watching of other stimuli in the immediate vicinity of the user. This lack of bodily movement is in comparison to control rats that appear more aggressive as they move about and attack more often. Because they were not experiencing the intoxication effects of either drug, control rats were less likely to remain inactive, as in the alert position.

5.1.6 Self-Grooming

The results of this behavioural measure also supported control rats being more aggressive than rats treated with either MA or BZP. This was evidenced by control rats exhibiting significantly more self-grooming in comparison to rats treated with either dose of MA or BZP. Again the dose-response profile was similar for both MA and BZP showing very

few occasions of self-grooming, thus suggesting less anxiety for these rats compared to control rats. These results along with the fact that rats treated with either MA or BZP adopted the aggressive posture, chased and sniffed the intruder rat significantly less often than control rats implied that less aggressive behaviour was being displayed.

5.1.7 Avoidance

Rats treated with saline or either dose of BZP did not attempt to avoid the intruder rat very often. However, rats treated with both doses of MA avoided the intruder rat significantly more often than control rats as well as rats treated with BZP. Although this could imply that both doses of MA caused an increase in aggressive behaviour, these results are possibly related to a slight increase in anxiety, as was observed for rats adopting the alert position behaviour. This increase in anxiety, but not in BZP treated rats across the same dose levels has been shown previously in a novel Y-maze (Herbert & Hughes, 2009). This is consistent with results from the alert position measure, which taken together may imply increased anxiety, but not elevated enough levels to result in aggression. Yet, as stated previously this possibility of increased anxiety was not supported by all results. The behavioural measures of self-grooming and actual time to approach the intruder rat suggested less anxiety in these MA- treated rats.

5.1.8 Up on Hind Legs

Results for this behaviour were similar to the avoidance and alert measures with an increase following administration of both MA and BZP (not for avoidance). This effect occurred for both doses of MA, but only for the low dose of BZP. Again, the increase in this behaviour may imply increased aggression as a result of being treated with MA or BZP, but this increase may have been mediated by other factors. These mediating factors include the

aforementioned maladaptive behavioural or psychological changes associated with intoxication from these drugs such as hyper-vigilance, psychomotor agitation and increased energy (Carlson, 2004; Julien, 2001). The experiencing of these symptoms might result in the rats moving about more often and investigating their cage by standing up on their hind legs, and being hyper-vigilant on what is occurring around them. This would seem to contradict results from the Alert Position behavioural measure where hyper-vigilance may have been displayed through the adoption of this position where there is no movement by the rat. Hyper-vigilance may be expressed in several different ways, of which both rapid scanning of the environment and watchfulness while immobile are both behavioural expressions.

In support of this result not being due to increased aggression is that this measure's outcome is not similar to results from the Aggressive Posture measure. It is possible that this response could be a prelude to Aggressive Posture because rats often began in this position before fighting or boxing each other (as in Aggressive Posture). If results from this measure implied increased aggression, then it would follow that a similar dose-response profile should have been observed for the Aggressive Posture measure as well (more occurrences of this behaviour for the two drugs). This did not happen because, although both doses of MA increased standing up on their hind legs facing each other, this was not so for the Aggressive Posture measure. For this latter measure, both doses of MA decreased the behaviour thereby indicating opposite effects of MA on these two behaviours. This of course does not support an increase in aggressive behaviour resulting from MA or BZP treatment. In addition, by adopting the Alert Position significantly less often than rats treated with either MA or BZP, control rats may have been more aggressive towards the resident rat, thus having less time to time to freeze in the alert position or to stand up on their hind legs facing the resident rat. Consequently, they may have been more inclined to fight whilst in this position. This is a

possibility that could be examined in future research by recording behaviours of the intruder rat as well.

5.2 Overall Discussion

Overall, the results do not suggest increased aggression following a single dose of MA (or indeed BZP), and thus support previous research that indicates chronic use is required for this to happen. This chronic use produces changes in normal neurotransmitter functioning, especially for DA and 5-HT through Hoaken and Stewart's (2003) neurotoxic damage to the brain. It is dysfunctioning of these neurotransmitters that results in aggression, especially *affective defence* (Weinshenker & Siegal, 2002) through paranoia and psychosis. It is this fact that provides support for a biological mechanism for the link between habitual MA use and aggression. An acute dose does not appear sufficient to produce the amount of change in monoamine functioning required for aggression to be evoked. The present results are consistent with previous research on acute doses of MA that found no resulting aggression (Miczek & O'Donnell, 1978; Richardson et al., 1972; Sokolov, et al., 2004; Sokolov & Cadet, 2006), but do not support studies such as that of Crowley (1972) in which aggression resulted from an acute dose. Because the present study only used two relatively low doses of MA, it is not possible to evaluate the dose dependent view of links between MA and aggression, which maintains that, the higher the dose, the greater the likelihood of aggressive behaviours occurring (Miczek & O'Donnell, 1978; Tyner & Fremouw, 2008). Of importance is that these low levels, in combination with the lack of prolonged and sustained exposure to the drugs, may not result in the serious changes and dysfunctioning in DA and 5-HT associated with mood changes and aggression.

Of the eight behavioural measures associated with aggression used in this study, only three resulted in a significant increase for rats treated with either MA or BZP (Alert Position,

Avoidance and Up on Hind Legs). Although, increases in these behaviours might imply increased aggression, it is also possible that they were due to effects of stimulant intoxication such as hyper-vigilance and higher drug-related anxiety, but not to a level that could result in aggressive behaviours. Any such increase in anxiety may be a result of the fight or flight mode, but again not to the extent where fighting results. If Alert Position, Avoidance and Up on Hind Legs were more indicative of anxiety than aggression, then along with the other measures that showed decreases for rats treated with either MA or BZP, the overall trend for the study as a whole was reduced drug-related aggression. Hence, the results did not support the view often portrayed by the media that a single dose (especially of MA) can result in adversely changed behaviour (Sheriden et al., 2006; Tyner & Fremouw, 2008).

5.2.1 Dose Levels/ MA versus BZP

For rats treated with MA, there were no consistent differences between the two doses in their effects. On the other hand, BZP produce a few differences between doses but one dose did not consistently increase or decrease the response more than the other i.e., a low dose of BZP resulted in significantly less sniffing of the intruder rat compared to a high dose, yet the same dose resulted in Alert Position being adopted significantly more often.

Although equivalent potency of the two drugs at each dose level could not be assumed, it was interesting to examine several differences between the two drugs. Overall, the visual presentation of results appeared similar when low and high dose responses were compared to saline and the corresponding dose level of the other drug, with no noticeable significant difference between drugs for both low and high dose levels. That is, when a low dose of MA resulted in a difference from the control group, the low dose of BZP produced a very similar result (and the same for high doses of both drugs).

The exceptions to this were results for the Avoidance and Up on Hind Legs measures. For both these, the dose-response profiles of the two drugs were qualitatively different from each other. For avoidance of the intruder rat, the administration of MA resulted in a significant increase in avoidance for both dose levels in comparison to the same level of BZP (ie., a low dose of MA versus a low BZP dose). This pattern occurred again for the resident rat standing up on its hind legs, with both doses of MA resulting in a significant increase in this behaviour compared to saline, but this time only the high dose of MA resulted in a significant difference to the high dose of BZP.

This similarity in patterns of results across both drugs supports previous research showing that BZP can result in similar patterns of behaviour to MA (Herbert & Hughes, 2009). This is also consistent with research showing that BZP's psychotropic effects on behaviour and neurochemistry may be indistinguishable from amphetamines because of their similar stimulant properties affecting DA and 5-HT (Aitchison & Hughes, 2006; Alansari & Hamilton, 2006; Baumann, et al., 2005; Brennan, et al., 2007; Fantegrossi et al., 2005; Gee et al., 2005; Gee & Fountain, 2007; Herbert & Hughes, 2009; Johnstone et al., 2007). This would also provide empirical data supporting the fact that BZP is not a safer option than MA.

5.3 Implications and Applications of Results

The relevance of these results to humans is the possibility that increasing the understanding of how these substances may affect human behaviour may help to reduce the significant costs associated with their use and abuse, as well as reducing the incorrect assumptions about their use. It is acknowledged that adolescence is a time of experimentation and that this often incorporates drug use, so a better understanding of how these drugs actually affect the user will help guide the diagnosis of a substance abuse problem and its treatment in this age group. By dispelling the incorrect assumption that a single use of MA

can result in permanent behavioural and psychological changes, the general public will also gain a more accurate awareness of the dangers of taking these drugs, especially when habitually used. The many adolescents who try these drugs once as part of growing up will be able to be better separated from those young people who have serious addiction problems and thus require more intensive treatment.

By adding support to previous research findings that suggest BZP may mirror MA in its psychotropic effects, results of the present study help emphasise the risk of exposure to the former drug. This will help the public become aware that BZP is not a safer option than better recognised 'hard drugs' such as MA. This could then result in people making more informed decisions when faced with using these drugs, as well as assisting policy makers in their efforts to produce laws for their control. Greater control, through an increased understanding may help to reduce the aforementioned significant costs to society through their use and abuse (Tyner & Fremouw, 2008).

Understanding that aggression associated with MA use is a result of chronic and not acute use can guide research in the study of chronic use, and how this persistent use of these drugs actually brings about dysfunctioning of DA and 5-HT. This may help to understand how these two neurotransmitters are associated with paranoia and psychosis which is in turn associated with aggression.

Results from this study may also provide information to enable a better understanding of the concept of ***affective defence*** and the many variations of how and under what circumstances it is displayed. This could then help researchers relate this to human examples of situations involving this type of aggression, and thus reduce the associated costs.

5.4 Limitations of this Study

There were several limitations to this research that may have influenced results. The first of these is the dose levels administered to the rats. Although dose levels used in this study are consistent with previous research that shows that 1mg/kg of MA is capable of invoking the release of DA and 5-HT required to illicit aggressive behaviours (Baumann et al., 2005; Brennan et al., 2007; Crowley, 1972), they may have not been strong enough to evoke aggression consistently through changes in DA and 5-HT resulting from toxicity to these neurotransmitters. This change in monoamine functioning is required to produce the paranoid psychosis associated with aggression (Boles & Miotto, 2003; Julien, 2001). However, in earlier studies involving acute doses of up to 7 and 8 mg/kg of MA, increased aggression still did not occur (Richards, et al., 1999; Sokolov & Cadet., 2006; Sokolov, et al., 2004). Addressing this issue of dose level, would also help to establish if there is indeed an argument for aggression occurring in a dose dependent manner (Miczek & O'Donnell, 1978; Tyner & Fremouw, 2008).

Another limitation may be the route of administration this study utilised, which was by way of intraperitoneal injection. Although MA administered by this route has been related to significantly more aggressive behaviour (Hall et al., 1996), substances such as MA and BZP are taken in a variety of ways by humans, such as inhalation through smoking, and orally. Differences in the rapidity of the onset of drug action could determine whether or not aggression results, as has been observed with crack cocaine and its equivalent form of MA, *Ice* (Julien, 2001). An example here is that inhalation through smoking MA results in a quicker and more intense effect than injection into the blood stream (Blanchard & Blanchard, 1999; McKetin et al., 2006).

Applying results from animal studies to humans may be another limitation of this current study. This is because of discrepancies in dose levels of drugs used across all the

research. Some researchers question the external validity of animal studies because contrary to other psychotropic drugs, lower doses of MA are typically adopted than what humans tend to use, resulting in animals having disproportionally lower blood concentration levels of the drug in comparison to humans (Tyner & Fremouw, 2008). Yet, in response to this limitation, it would be unethical to use humans in a study such as this which would involve participants taking illicit substances and then indulging in aggressive behaviours aimed at causing harm to another.

The timing of adolescence was also an area of possible weakness in this research. Although research acknowledges that PND 41 to 50 in rats is often regarded as equivalent to adolescence in humans (Smith, 2003; Spear, 2007a), there is considerable variation in opinions of when exactly adolescence occurs across species and sexes (Spear, 2007b). These differences in when adolescence actually occurs can result from individual differences in maturity, brain development and temperament. While some will develop these aspects at an early age, some may not have equal development until a much later age. These differences could then impact on results from behavioural testing by providing large variations in results for this age group. This could in turn cause behavioural differences to be attributed to manipulated variables (such as drug dose) instead of individual age differences.

Also of relevance is the breed of rats. The PVG/C hooded rats used in the present study are known for their docile nature and low activity in relation to other breeds. Even though this may make them easier to handle and a popular breed to use in experimentation, it may reduce their natural inclination to be active and aggressive (Animal Research Centre, 2010).

5.5 Strengths of this Study

Strengths of this study include the utilisation of an empirically supported test of aggression. The Resident/Intruder test of aggression has been cited as a good measure of

affective defence, or *territorial* aggression, and has been used successively by many previous researchers in combination with the responses recorded in the present study (Johns & Noonan, 1995; Miczek, & O'Donnell, 1978; Sgoifo et al., 1996; Sokolov, & Cadet, 2006; Weinshenker & Siegal, 2002). In support of this test being a strength for this study is that all eight measures used occurred during testing. The fact that often these behaviours were performed by both the resident/focal rat, and the intruder rat, show their validity through their regular occurrences. An invalid behavioural measure would most likely not have occurred very often, and would also not likely have been observed by both focal and intruder rats.

Purity of drugs is another methodological strength of this study. In real life scenarios it is rare to find a pure form of a drug as many recreational drugs are made with ingredients that are easy to procure. This is especially relevant for MA which is made in clandestine laboratories, and can be synthesised from general household products such as iodine and sodium hydroxide found in drain cleaners, and ephedrine and pseudoephedrine which are found in over-the-counter cold and flu remedies (McFadden, & Matuszewich, 2007; New Zealand Police 2009; Tyner & Fremouw, 2008; Volkow et al., 2001; Wilkins et al., 2009). This can result in 'dirty drugs' containing many different substances, all of which may have different effects on the user (Fergusson et al., 2008). This current study used MA which was donated in a pure crystal form by Environmental Science & Research Limited (ESR, Wellington, New Zealand), and pure research-grade BZP purchased from ABRC Gmbh & Co, Karlesruhe, Germany. This ensured that the drugs used were not contaminated by foreign substances thereby ensuring that the results were truly associated with the drug itself and not confounded by other ingredients.

Controlling for other possible confounding factors through the use of an animal model of aggression was another strength of this study. This is because the rats used were all housed in a contained environment in an animal facility, which allowed other extraneous factors

acknowledged to influence the relationship between drug use and aggression in humans to be eliminated. Examples of these extraneous factors are childhood exposure to drug use, lack of parental control and attachment issues (Chassin, Ritter, Trim, & King, 2003). This again enabled the results to be related more precisely to the effects of the drug, and not to other factors. Consequently, the results are more likely to be relevant to a biological basis for any drug/aggression relationship involving *Psychopharmacological Violence* rather than *Systemic* or *Economic Compulsive Violence* (Boles & Miotto, 2003).

Another strength of this study, related to both purity of drug, and confounding factors, is that any resulting aggression, or lack of, could be attributed to the principle use of MA or BZP. These drugs are mainly used in conjunction with other drugs such as marijuana, and this could determine whether or not aggression develops as a consequence of chronic use (Fergusson, et al., 2008). The other drugs being used could affect monoamine functioning as well. Because this study guaranteed no previous drug use by the participants, the results were attributable only to the action of MA or BZP.

5.6 Suggestions for Future Research

To address some of the limitations of this study, and to help provide an increased understanding of how MA and BZP use is associated with aggression, several initiatives could be adopted in future research. Firstly, defaecation frequency of the resident rat could be measured to determine if it is more fearful or not, or is in a state of high emotional reactivity (Aitchison & Hughes, 2006; Anderson & Hughes, 2008). An increase in numbers of faecal boluses has been associated with greater fear and anxiety which in turn can lead an increase in aggressiveness as a response to this heightened emotional state.

In addition, higher doses could be administered to see if aggression does occur in a dose-dependent manner thereby enabling determination of the critical dose for the production

of aggression through changes in monoamine functioning (quantitative). This would enable determination of the toxic levels of MA and BZP which result in the paranoia and psychosis associated with chronic use.

With respect to to the toxicity of chronic use in relation to DA and 5-HT, it would be interesting to measure these transmitters after an acute dose, and then subsequently after the development of dependence from chronic use, followed by withdrawal when the rat is no longer exposed to the drug. This would allow a systematic tracking of the changes in their functioning resulting from increased toxicity from the chronic use of these drugs. This in turn could provide a better understanding of the level of these drugs needed in the brain to produce this toxicity and resulting dysfunctioning in these monoamines. Testing aggressiveness during withdrawal, and then after a period of abstinence could help researchers observe if the damage to the functioning of the transmitters is reversible through a decrease in aggressive behaviour.

In future research it would be useful to record the responses of the intruder rat because in the present study, the intruders often appeared to be more aggressive than the resident rats in terms of the frequencies of the responses recorded for the residents. Recording behaviour of the intruder as well as the resident rat would provide more information, and sample more subtypes of aggression. In doing this, not only would aggressive behaviours associated with affective defence be observed (such as *inter-male*, *sex-related* and *territorial),* but predatory aggression could also be observed because of an intruder rat's tendency to be aggressive when not protecting its own territory. Observing both the intruder and resident rat could provide more information about behaving aggressively while under the influence of substances.

Including sex differences would also be of interest as a female rat may react differently to an intruder in her home cage, especially if she was pregnant or was defending her pups.

Inclusion of females would also allow a comparison of sex differences for these drugs, as it is likely that both MA and BZP would affect males differently to females, as has been shown in previous research on a variety of psychotropic drugs (Hughes, 2007).

5.7 Conclusion

The results from the present study support the view that an acute dose of either MA or BZP will not result in aggression. The association between MA use and aggression is acknowledged to result from chronic use resulting in dysfunctioning of the neurotransmitters, DA and 5-HT, which in turn leads to paranoia and psychosis through the drug's toxic effects. These neurotransmitters are especially susceptible to the influences of drugs in the adolescent years when natural change is occurring, and the experimentation with drugs begins to occur. This age group are also associated with a large volume of violent and aggressive crime, causing high costs to society.

Although individual differences mean that there will be an occasional person who experiences mood altering properties from an acute dose of MA (Boles & Miotto, 2003), in general, an acute dose does not appear to affect these neurotransmitters to the extent that changes in aggressive behaviour are apparent. What may result from an acute dose of MA or BZP is behaviour associated with experiencing a euphoric high and pleasure from the first exposure to these stimulant drugs. This would involve hyper-vigilance, increased alertness and psychomotor agitation. As a result of this, instead of increasing aggression, an acute dose may in fact reduce the chances of aggressive behaviour through the euphoric high and novel experience which supersedes fear or feelings of threat resulting in affective defensive aggressive behaviours. Once the user habituates to this and thus requires more drug to get the same effect, the aforementioned changes in monoamine functioning combine to cause the paranoia and psychosis involved in misinterpreting others intentions and thus aggression.

With respect to BZP, it appears that this drug may indeed produce similar effects to MA, and thus, is not necessarily a safer option than MA. The possible detrimental effects of longer-term use these two drugs can not be ignored, but to date there is no support for such effects being caused by a single dose of either drug.

References

Aitchison, L. K., & Hughes, R. N. (2006). Treatment of adolescent rats with 1-benzylpiperazine: a preliminary study of subsequent behavioural effects. *Neurotoxicology & Teratology, 30,* 195 – 201.

Alansari, M., & Hamilton, D. (2006). Nephrotoxicity of BZP-based herbal party pills: a New Zealand case report. *The New Zealand Medical Journal, 119*(1233).

Anderson, S. L. (2005). Stimulants and the developing brain. *Trends in Pharmacological Sciences, 26*, 237-243.

Anderson, N. L. & Hughes, R. N. (2008). Increased emotional reactivity in rats following exposure to caffeine during adolescence. *Neurotoxicology and Teratology, 30,* 195–201

Animal Resources Centre. (2010). Retrieved January 27, 2010, from http://www.arc.wa.gov.au/service.php?category=Inbred+Rats.

Armstrong, T. D., & Costello, E. J. (2002). Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *Journal of Consulting and Clinical Psychology, 70*, 1224-1239.

Austin, A. A. (2004). Alcohol, tobacco, other drug use, and violent behaviour among native Hawaiians: ethnic pride and resilience. *Substance Use and Misuse, 39*, 721-746.

Austin, J. T., & Villanova, P. (1992). The criterion problem. *Journal of Applied Psychology, 77*, 836-874.

Baskin-Sommers, A., & Sommers, I. (2006). The co-occurrence of substance use and high-risk behaviors. *Journal of Adolescent Health 38,* 609-611.

Baumann, M. H., Clark, R. D., Budzynski, A. G., Partilla, J. S., Blough, B. E., & Rothman. R. B. (2005). *N*-Substituted piperazine abused by humans mimic the molecular mechanism of 3,4-Methylenedioxymethamphetamine (MDMD, or 'Ecstasy'). *Neuropsychopharmacology, 30,* 550-560.

Blanchard, D. C., & Blanchard, R. J. (1999). Cocaine potentiates defensive behaviours related to fear and anxiety. *Neuroscience and Biobehavioral Reviews, 23,* 981-991.

Boles, S. M. & Miotto, K. (2003). Substance abuse and violence. A review of the literature. *Aggression and Violent Behavior, 8,* 155-174.

Bondar, N. P., & Kudryavtseva, N. N. (2005). The effects of the D_1 receptor antagonist SCH-23390 on individual and aggressive behaviour in male mice with different experience of aggression. *Neuroscience and Behavioral Physiology, 35,* 221-227.

Brecht, M. L., O'Brien, A., von Mayrhauser, C., & Anglin, M. D. (2004). Methamphetamine use behaviours and gender differences. *Addictive Behaviors, 29,* 89-106.

Brems, C., & Johnson, M. E. (2001). What every clinician needs to know about substance abuse. *Journal of Psychological Practice, 7,* 1-22.

Brennan, K., Johnstone, A., Fitzmaurice, P., Lea, R., & Schenk, S. (2007). Chronic benzylpiperazine (BZP) exposure produces behavioural sensitization and cross-sensitization to methamphetamine (MA). *Drug and Alcohol Dependence, 88,* 204-213.

Butler, R., Wheeler, A., & Sheridan, J. (2009). Physical and psychological harms and health consequences of methamphetamine use amongst a group of New Zealand users. *International Journal of Mental Health Addiction.* DOI 10.1007/s11469-009-9213-5

Campbell, H., Cline, W., Evans, M., Lloyd, J., & Peck. A. W. (1973). Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts. *European Journal of Clinical Pharmacology, 6,* 170-176.

Carlson, N.R. (2004). *Physiology of behavior* (8th ed.). Boston: Allyn and Bacon.

Cartier, J., Farabee, D., & Prendergast, M. L. (2006). Methamphetamine use, self-reported violent crime, and recidivism among offenders in California who abuse substances. *Journal of Interpersonal Violence, 21,* 435-445.

Cancela, L. M., Basso, A. M., Martijena, I. D., Capriles, N. R., & Molina, V. A. (2001). A dopaminergic mechanism is involved in the 'anxiogenic-like' response induced by chronic amphetamine treatment: A behavioral and neurochemical study. *Brain Research, 909,* 179-186.

Chambers, R. A., Taylor, J. R., & Potenza, M. N. (2003). Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *The American Journal of Psychiatry, 160,* 1041-1052.

Chassin, L., Ritter, J., Trim, R. S., & King, K. M. (2003). Adolescent substance use disorders. In E. J. Mash, & R. A. Barkley (Eds.), *Child psychopathology* (2nd ed.). The Guildford Press: New York.

Chong, J. (2007). *Youth justice statistics in New Zealand: 1992-2006.* Wellington: Ministry of Justice.

Clingempeel, W. G., Britt, S. C., & Henggeler, S. W. (2008). Beyond treatment effects: comorbid psychopathologies and long-term outcomes among substance-abusing delinquents. *American Journal of Orthopsychiatry, 78*, 29-36.

Cohen, R., Hsueh, Y., Russell, K. M., & Ray, G. E. (2006). Beyond the individual: a consideration of context for the development of aggression. *Aggression and Violent Behavior, 11*, 341-351.

Couppis, M. H., & Kennedy, C. H. (2008). The rewarding effect of aggression is reduced by nucleus accumbens dopamine receptor antagonism in mice. *Psychopharmacology, 197*, 449-456.

Craske, M. G., & Barlow, D. H. (2008). Panic disorder and agoraphobia. In D. H. Barlow (Ed.), *Clinical handbook of psychological disorders. A step by step treatment manual* (4th ed.). The Guildford Press: New York.

Crowley, T. J. (1972). Dose-dependent facilitation or suppression of rat fighting by methamphetamine, phenobarbital, or imipramine. *Psychopharmacologia, 27*, 213-222.

Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug and Alcohol Review, 27*, 253-262.

Davis, W. M. (1996). Psychopharmacologic violence associated with cocaine abuse: kindling of a limbic dyscontrol syndrome? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 20*, 1273-1300.

Fantegrossi, W. E., Winger, G., Woods, J. H., Woolverton, W. L., & Coop, A. (2005). Reinforcing and discriminative stimulus effects of 1-benzylpiperazine and trifluoromethylphenylpiperazine in rhesus monkeys. *Drug and Alcohol Dependence, 77,* 161-168.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study. *Drug and Alcohol Dependence, 96,* 165-177.

Fields, S. A., & McNamara, J. R. (2003). The prevention of child and adolescent violence: a review. *Aggression and Violent Behavior, 8,* 61-91.

Frick, P. J., Cornell, A. H., Barry, C. T., Bodin, S. D., & Dane, H. E. (2003). Callous-unemotional traits and conduct problems in the prediction of conduct problem severity, aggression, and self-report of delinquency. *Journal of Abnormal Child Psychology, 31*, 457-470.

Friedman, A. S. (1998). Substance use/abuse as a predictor to illegal and violent behaviour: a review of the relevant literature. *Aggression and Violent Behavior, 3,* 339-355.

Gee, P., Richardson, S., Woltersdorf, W., & Moore, G. (2005). Toxic effects of BZP-based party pills in humans: a prospective study in Christchurch, New Zealand. *The New Zealand Medical Journal, 118*(1227).

Gee, P., & Fountain, J. (2007). Party on? BZP party pills in New Zealand. *The New Zealand Medical Journal, 120*(1249).

Grimes, J. M., Ricci, L., Rasakhan, K., & Melloni Jr, R. H. (2006). Drugs of abuse and aggression. In R.J. Nelson (Ed.), *Biology of Aggression* (pp. 371 – 424). United States: Oxford University Press.

Hales, J., & Manser, J. (2007). *New Zealand Police, NZ-ADAM Annual Report.* Health Outcomes International Pty Ltd.

Hall, W., Hando, J., Darke, S., & Ross, J. (1996). Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. *Addiction, 91,* 81-87.

Hare, R. D., & Mcpherson, L. M. (1984). Violent and aggressive behaviour by criminal psychopaths. *International Journal of Law and Psychiatry, 7,* 35-50.

He, J., Xu, H., Yang, Y., Zhang, X., & Li, X. (2005). Chronic administration of quetiapine alleviates the anxiety-like behavioural changes induced by a neurotoxic regimen of *dl*-amphetamine in rats. *Behavioural Brain Research, 160,* 178-187.

Herbert, C. E., & Hughes, R. N. (2009). A comparison of 1-benzylpiperazine and methamphetamine in their acute effects on anxiety-related behavior of hooded rats. Pharmacology, Biochemistry and Behavior, 92, 243-250.

Hinshaw, S. P., & Lee, S. S. (2003) Conduct and oppositional defiant disorders. In E. J. Mash & R. A. Barkley (Eds.), *Child psychopathology* (2nd ed.). The Guilford Press, New York.

Higgins, S. T., & Katz, J. L. (1998). *Cocaine abuse: behaviour, pharmacology, and clinical applications.* San Diego: Academic Press.

Hoaken, P. N. S., & Stewart, S. H. (2003). Drugs of abuse and the elicitation of human aggressive behaviour. *Addictive Behaviors, 28,* 1553-1554.

Homer, B. D., Solomon, T. M., Moeller, R.W., Mascia, A., DeRaleau, L., & Halkitis, P. N. (2008). Methamphetamine abuse and impairment of social functioning: a review of the underlying neurophysiological causes and behavioural implications. *Psychological Bulletin, 134*, 301-310.

Hughes, R. N., & Greig, A. M. (1976). Effects of caffeine, methamphetamine and methylphenidate on reactions to novelty and activity in rats. *Neuropharmacology, 15,* 673-676.

Hughes, R. N. (2007). Sex does matter: comments on the prevalence of male-only investigations of drug effects on rodent behaviour. *Behavioral Pharmacology, 18,* 583-589.

Johns, J. M., & Noonan, L. R. (1995). Prenatal cocaine exposure affects social behaviour in Sprague-Dawley rats. *Neurotoxicology and Teratology, 17*, 569-576.

Johnstone, A. C., Lea, R. A., Brennan, K. A., Schenk, S., Kennedy, M. A., Fitzmaurice, P. S. (2007). Review: benzylpiperazine: a drug of abuse? *Journal of Psychopharmacology, 21,* 888 – 894.

Julien, R. M. (2001). *A primer of drug action: a concise, nontechnical guide to the actions, uses and side effects of psychoactive drugs, revised and updated*. New York: W.H. Freeman and Company.

Lansford, J. E., Erath, S., Yu, T., Pettit, G. S., Dodge, K. A., & Bates, J. E. (2008). The developmental course of illicit substance use form age 12 to 22: links with depressive, anxiety, and behaviour disorders at age 18. *The Journal of Child Psychology and Psychiatry, 49*, 877-885.

London, E. D., Simon, S. L., Berman, S. M., Mandelkern, M. A., Lichtman, A. M., Braman, J., et al. (2004). Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Archives of General Psychiatry, 61,* 73-84.

Long, S. F., Wilson, M. C., Sufka, K. J., & Davis, W. M. (1996). The effects of cocaine and nandroline co-administration on aggression in male rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 20,* 839-856.

Malkesman, O., Maayan, R., Weizman, A., & Weller, A. (2006). Aggressive behaviour and HPA axis hormones after social isolation in adult rats of two different genetic animal models for depression. *Behavioural Brain Research, 175,* 408-414.

Maxwell, J. (2005). Emerging research on methamphetamine. *Current Opinion in Psychiatry, 18,* 235-242.

McCormick, R. A., & Smith, M. (1995). Aggression and hostility in substance abusers: the relationship to abuse patterns, coping style, and relapse triggers. *Addictive Behaviors, 20,* 555-562.

McEllistrem, J. E. (2004). Affective and predatory violence: a bimodal classification system of human aggression and violence. *Aggression and Violent Behavior, 10,* 1-30.

McKetin R., McLaren, J., Riddell, S., & Robins, L. (2006). The relationship between methamphetamine use and violent behaviour. *Crime and Justice Bulletin,* (97).

McFadden, L. M., & Matuszewich, L. (2007). The effects of methamphetamine exposure during preadolescence on male and female rats in the water maze. *Behavioural Brain Research, 185,* 99-109.

Ministry of Health. (1975). Misuse of Drugs Act 1975. Retrieved January 22, 2010, from http://www.legislation.govt.nz/act/public/1975/0116/latest/DLM436508.html

Miczek, K. A., & O'Donnell, J. M. (1978). Intruder-evoked aggression in isolated and nonisolated mice. Effects of psychomotor stimulants and L-dopa. *Psychopharmacology, 57*, 47-55.

Miczek, K. A., Fish, E. W., de Bold, J. F., de Almeida, R. M. M. (2002). Social and neural determinants of aggressive behaviour: pharmacotherapeutic targets at serotonin, dopamine and y-aminobutyric acid systems. *Psychopharmacology, 163*, 434-458.

Miura, H., Fuliki, M., Shibata, A., & Ishikawa, I. (2006). Prevalence and profile of methamphetamine users in adolescents at a juvenile classification home. *Psychiatry and Clinical Neurosciences, 60*, 352-357.

New Zealand Department of Corrections (2003). *Census of prison inmates and home detainees*. Retrieved February 10, 2009, from http://www.corrections.govt.nz/research/census-of-prison-inmates-and-home-detainees/census-of-prison-inmates-and-home-detainees-2003.html

New Zealand Police. (2009). *New Zealand police illicit drug strategy to 2010.* Retrieved January, 19, 2010, from http://www.police.govt.nz/resources/2009/NZ_Police_Illicit_Drug_Strategy_2009.pdf

Parrott, D. J., Giancola, P. R. (2007). Addressing "the criterion problem" in the assessment of aggressive behaviour: development of a new taxonomic system. *Aggression and Violent Behavior, 12*, 280-299.

Payer, D. E., Lieberman, M. D., Monterosso, J. R., Xu, J., Fong, T. W., & London, E. D. (2008). Differences in cortical activity between methamphetamine-dependent and healthy individuals performing a facial affect matching task. *Drug and Alcohol Dependence, 93*, 93-102.

Pellegrini, A. D. (2002). Affiliative and aggressive dimensions of dominance and possible functions during early adolescence. *Aggression and Violent Behavior, 7,* 21-31.

Police National Headquarters (2007). *New Zealand Crime Statistics: a summary of recorded and resolved offence statistics.* Retrieved January, 28, 2009, from http://www.police.govt.nz/service/statistics/2008/fiscal/00_National_07-08_Official_Stats_Final.pdf

Police National Headquarters (2009). *New Zealand crime statistics2008: a summary of recorded and resolved offence statistics.* Retrieved January 10, 2010, from http://www.police.govt.nz/service/statistics/2008/calendar/00_National_Official_Stats_2008_Final.pdf

Ramirez, J. M. (2003). Hormones and aggression in childhood and adolescence. *Aggression and Violent Behavior, 8*, 621-644.

Richards, J. R., Bretz, S. W., Johnson, E. B., & Turnipseed, S. D., Brofeldt, B. T., & Derlet, R. W. (1999). Methamphetamine abuse and emergency department utilization. *The Western Journal of Medicine, 170*, 198-202.

Richardson, D., Karczmar, A. G., & Scudder, C. L. (1972). Intergeneric behavioural differences among methamphetamine treated mice. *Psychopharmacologia, 25*, 347-375.

Rothman, R. B., & Baumann, M. H. (2003). Monoamine transporters and psychostimulant drugs. *European Journal of Pharmacology, 479*, 23-40.

Seddon, T. (2000). Explaining the drug-crime link: theoretical, policy and research issues. *Journal of Social Policy, 29*, 95-107.

Sekine, Y., Ouchi, Y., Takei, N., Yoshikawa, E., Nakamura, K., Futatsubashi, M., et al. (2006). Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. *Archives of General Psychiatry, 63*, 90-100.

Sgoifo, A., De Boer, S. F., Haller, J., & Koolhaas, J. M. (1996). Individual differences in plasma catecholamine and corticosterone stress responses of wild-type rats: relationship with aggression. *Archives of General Psychiatry, 60*, 1403 – 1407.

Simpson, A. I. F., Brinded, P. M. J., Laidlaw, T. M., Fairley, N., & Malcolm, F. (1999). *The national study of psychiatric morbidity in New Zealand prisons; an investigation of the prevalence of psychiatric disorders among New Zealand inmates*. Department of Corrections. Retrieved February, 10, 2010, from http://www.corrections.govt.nz/__data/assets/pdf_file/0006/176424/nationalstudy.pdf

Sheridan, J., Bennett, S., Coggan, C., Wheeler, A., & McMillan, K. (2006). Injury associated with methamphetamine use: a review of the literature. *Harm Reduction Journal, 3*(14).

Smith, R. F. (2003). Animal models of periadolescent substance abuse. *Neurotoxicology and Teratology, 25*, 291-301.

Sokolov, B. P., Schindler, C. W., & Cadet, J. L. (2004). Chronic methamphetamine increases fighting in mice. *Pharmacology, Biochemistry and Behavior, 77*, 319-326.

Sokolov, B. P., & Cadet, J. L. (2006). Methamphetamine causes alterations in the MAP kinase-related pathways in the brains of mice that display increased aggressiveness. *Neuropsychopharmacology, 31,* 956-966.

Spear, L. (2007a). The developing brain and adolescent-typical behaviour patterns: An evolutionary approach. In D. Romer & E.F. Walker (Eds.), *Adolescent psychopathology and the developing brain. Integrating brain and prevention science*. Oxford University Press: Oxford.

Spear, L. P. (2007b). Assessment of adolescent neurotoxicity: rationale and methodological considerations. *Neurotoxicology and Teratology, 29,* 1-9.

Stansfield, K. H., & Kirstein, C. L. (2005). Neurochemical effects of cocaine in adolescence compared to adulthood. *Developmental Brain Research, 159,* 119-125.

Statistics New Zealand (STANZ, 2006). *Crime in New Zealand: 1996 – 2005*. Wellington: New Zealand. Retrieved January, 11, 2010, from http://www.stats.govt.nz/reports/analytical-reports/crime-in-nz-96-05.aspx

Tyner, E. A., & Fremouw, W. J. (2008). The relation of methamphetamine use and violence: a critical review. *Aggression and Violent Behavior, 13,* 285-297.

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Leonido-Yee, M., Franceschi, D., et al. (2001). Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *American Journal of Psychiatry, 158,* 377-382.

Vorhees, C. V., Reed, T. M., Morford, L. L., Fukumura, M., Wood, S. L., Brown, C. A., et al. (2005). Periadolescent rats (P41-50) exhibit increased susceptibility to D-

methamphetamine-induced long term spatial and sequential learning deficits compared to juvenile (P21-30 or P31-40) or adult rats (P51-60). *Neurotoxicology and Teratology, 27*, 117-134.

Weinshenker, N. J. & Siegal, A. (2002). Bimodal classification of aggression: affective defence and predatory attack. *Aggression and Violent Behavior, 7*, 237 – 250.

Wilkins, C., Griffiths, R., & Sweetsur, P. (2009). *Recent trends in illegal drug use in New Zealand, 2006 – 2008. Findings from the 2006, 2007 and 2008 Illicit Drug Monitoring System (IDMS).* Centre for Social and Health Outcomes Research and Evaluation: Auckland. Retrieved February, 10, 2010, from http://www.shore.ac.nz/projects/2008_IDMS_executive_summary.pdf

Wilkins, C., Rose, E., Trappitt, D., Adamson, S., & DeZwart, K. (2004). *Recent changes in the methamphetamine scene in New Zealand: Preliminary findings from key informant surveys of drug enforcement officers and drug treatment workers*. Retrieved February, 10, 2010, from http://www.police.govt.nz/resources/2004/meth-scene/index.html

Wilkins, C., Girling, M., Sweetsur, P., & Butler, R. (2005). Key Findings from the Methamphetamine Module of the 2005 Illicit Drug Monitoring System (IDMS). Retrieved January, 19, 2010, from http://www.ndp.govt.nz/moh.nsf/pagescm/1078/$File/idmsmethamphetamines.pdf

Wilkens, C., Sweetsur, P., & Casswell, S. (2006). Recent population trends in amphetamine use in New Zealand: comparisons of findings from national household drug surveying in 1998, 2001 and 2003. *The New Zealand Medical Journal, 119*(1244).

Wu, L. T., Pilowsky, D. J., Schlenger, W. E., & Galvin, D. M. (2007). Misuse of methamphetamine and prescription stimulants among youths and young adults in the community. *Drug and Alcohol Dependence, 89*, 195-205.

Zweben, J., Cohen, J., Christian, D., Galloway, G., Salinardi, M., Parent, D., et al. (2004). Psychiatric symptoms in methamphetamine users. *American Journal on Addictions, 13*, 181-190.

Appendix A

AEC Ref: 2008/21R

12 September

Mr Hamish Johnson
46 Parkstone Avenue
Ilam
CHRISTCHURCH

Dear Hamish

I am pleased to inform you that the Animal Ethics Committee (AEC) has approved your application entitled: "The acute effects of methamphetamine and 1-benzylpiperazine on aggressive behaviour"

Approval has been granted:

(a) for the use of 150 animals
(b) for your research project to be undertaken over a period of 7 months from 1 October 2008 to 30 April 2009. If you require an extension of this period please contact the AEC Secretary.

As part of AEC's new Code of Ethical Conduct all applicants receiving approval to work on animals are required to provide a final report at the completion of their project. The purpose is to provide the AEC with a record of your use of animals and what was achieved by your research project. We are very much interested in your findings and to learn what you have achieved. Following the completion date indicated above you are asked to provide this report using the new Final Report form which is available at the AEC web site (https://intranet.canterbury.ac.nz/research/ethics.shtml).

On an annual basis the University is legally required to provide to MAF statistical data on all animal manipulations undertaken in a calendar year. To assist us in collating this information you are also required to complete and return to the AEC Secretary the attached MAF Animal Manipulation Statistical form 30 days after the completion of this project, or once every three years, which ever comes first. If no animals have been manipulated in your project please provide a "Nil" return. Please also find enclosed a copy of the Animal Welfare (Records and Statistics) Regulations 1999 for your information, together with a list of Animal Type Codes and brief guideline notes for your assistance.

Yours sincerely

Associate Professor Lou Reinisch
Acting Chair
Animal Ethics Committee

cc Animal Ethics Committee

Appendix B

Group Number:	**Group Name:** **(eg. 1mg/kg-Methamphetamine-R/I 1st)**	**Rat:**	**Test:**
Aggressive Behaviour	**Operational Definition**		
Latency Time to Attack (LTA):	first instance (measured in seconds) of movement by the focal/resident rat towards the stimulus/intruder rat of a distance greater than the length of a rat, resulting in near or actual contact. Includes:	**Frequency**	**Extra comments**
Aggressive Posture	the focal rat restraining the intruder with front paws, either holding down other rat or up on hind legs "boxing" with other rat		
General contact/near contact	First move resulting in near contact or contact not involving above two actions		
	NOTE: record duration of all instances of above behaviours		
Chase: **Sniffing**	any pursuit of stimulus/intruder rat around cage by the focal/resident rat -stops as soon as the focal rat stops moving, or contact is made (does not include first contact-see above) – focal rat must chase over a distance equivalent to length of a rat - must include stimulus/intruder rat *moving away* from focal rat (so not just a move by focal rat towards other rat (this would be *LTA-aggressive posture* above) any aggressive sniffing of anus/genital region (this may/may not include use of paws) - **record duration of instances** – instance stops when sniffing stops for 1 second		
Alert position:	focal rat exhibits a sudden interruption of all movement with head directed towards stimulus/intruder rat-must be perfectly still for at least 1 second duration (must be facing other rat - not upwards or to side)		
Self-groom:	the resident/focal rat grooms itself by licking body fur and/or face washing (most often after a fight attack). Instance will cease when ever the grooming stops for more than 1 second.		
Avoidance	Any move greater than the length of a rat that the focal/resident rat makes to escape or distance itself from the intruder/stimulus rat. Instance stops when movement stops for more than 1 second		
Standing on Hind Legs	Any instance when focal/resident rat stands up on hind legs and faces stimulus/intruder rat - does not include when rat is doing this to look out top of cage – DOES NOT include contact with other rat		

Appendix C

Aggressive Posture		
	Methamphetamine	
	Mean	SEM
Saline	5.83	1.61
1mg/kg	.33	.33
2mg/kg	.50	.34
	1-Benzylpiperazine	
10mg/kg	.50	.23
20mg/kg	.92	.38
General/ Non-Aggressive		
	Methamphetamine	
	Mean	SEM
Saline	104.94	55.18
1mg/kg	19.46	5.30
2mg/kg	23.73	4.48
	1-Benzylpiperazine	
10mg/kg	36.03	11.14
20mg/kg	13.65	2.57
Chase		
	Methamphetamine	
	Mean	SEM
Saline	5.5	1
1mg/kg	2.17	.46
2mg/kg	2.42	.40
	1-Benzylpiperazine	
10mg/kg	1.83	.61

20mg/kg	1.83	.47
Sniffing		
	Methamphetamine	
	Mean	SEM
Saline	13.42	1.79
1mg/kg	4.42	1.32
2mg/kg	4	.85
	1-Benzylpiperazine	
10mg/kg	2.25	.54
20mg/kg	7.33	2.04
Alert Position		
	Methamphetamine	
	Mean	SEM
Saline	1.25	.30
1mg/kg	3.5	.73
2mg/kg	2.67	.77
	1-Benzylpiperazine	
10mg/kg	4.67	.1.04
20mg/kg	2.25	.57
Self-Grooming		
	Methamphetamine	
	Mean	SEM
Saline	3.67	1.12
1mg/kg	.92	.26
2mg/kg	1.08	.26
	1-Benzylpiperazine	
10mg/kg	1.08	.31
20mg/kg	1.08	.53

Avoidance		
	Methamphetamine	
	Mean	SEM
Saline	1.83	.39
1mg/kg	6	.88
2mg/kg	6.58	1.75
	1-Benzylpiperazine	
10mg/kg	1.75	.45
20mg/kg	1.92	.48
Up on Hind Legs		
	Methamphetamine	
	Mean	SEM
Saline	.75	.28
1mg/kg	4.75	1.18
2mg/kg	4.75	.96
	1-Benzylpiperazine	
10mg/kg	3	.85
20mg/kg	2.25	.55