Contribution of Impulsivity and Serotonin Receptor Neuroadaptations to the Development of an MDMA ('Ecstasy') Substance Use Disorder

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Abstract As is the case with other drugs of abuse, a proportion of ecstasy users develop symptoms consistent with a substance use disorder (SUD). In this paper, we propose that the pharmacology of MDMA, the primary psychoactive component of ecstasy tablets, changes markedly with repeated exposure and that neuroadaptations in dopamine and serotonin brain systems underlie the shift from MDMA use to MDMA misuse in susceptible subjects. Data from both the human and laboratory animal literature are synthesized to support the idea that (1) MDMA becomes a less efficacious serotonin releaser and a more efficacious dopamine releaser with the development of behaviour consistent with an SUD and (2) that upregulated serotonin receptor mechanisms contribute to the development of the MDMA SUD via dysregulated inhibitory control associated with the trait of impulsivity.

Keywords MDMA · Ecstasy · Substance use disorder · Serotonin · Dopamine · Inhibitory control · Impulsivity

Contents

Most drugs are initially used in a relatively controlled manner, but over time a pattern of uncontrolled and compulsive use can develop. This change in drug-taking from controlled to uncontrolled is accompanied by the development of pronounced drug-seeking behaviour. When someone takes a drug repeatedly, they form a strong association between the drug and its rewarding properties. The initial drug-taking is based primarily on these rewarding drug effects. With continued factors that accompany drug-taking (images, smells, people, paraphernalia) become associated

with that same, rewarding, response. Mere exposure to these cues can then produce an intense craving and relapse, even in detoxified users. This is perhaps the most insidious aspect of drug misuse—the craving for drugs that leads to drug-taking and then more drug-seeking, leading to the vicious cycle of uncontrolled use that defines a substance use disorder (SUD).

We know that the shift to drug misuse is accompanied by changes in brain systems underlying motivation, learning, memory and reinforcement (Volkow and Baler 2014). Many studies have identified the brain chemical, dopamine (DA), as critical for the development and maintenance of drug-taking (Koob and Volkow 2010; Weiss et al. 1992), and activity in DA systems codes the significance of rewarding events. With repeated drug exposures, the contexts in which drugs are experienced begin to play a role in drug-seeking and drug-taking (Di Ciano and Everitt 2004; Everitt et al. 2008). Responses to physiologically relevant stimuli are decreased, while responses to stimuli that have been associated with drug-taking become enhanced (Everitt and Robbins 2005). Drugs of abuse begin to activate 'habit' circuitry in the brain that automatically, and preferentially, guides behaviour towards drugs (Everitt and Robbins 2005; Kalivas 2008). At the same time, there is a failure to inhibit behaviours that are associated with pathological drug-seeking (Kalivas 2008). Thus, there are persistent changes in brain circuitry so that drug-related stimuli initiate drug-seeking behaviour, while brain circuits that underlie inhibitory control and executive functioning become dysfunctional.

Acute exposure to MDMA increases synaptic levels of DA, like other amphetamines. It also stimulates the release of 5-HT, like other amphetamines. Unlike other amphetamines, however, MDMA preferentially stimulates release of serotonin (5-HT) with much smaller increases in synaptic DA (see Schenk 2011 for a review). Selective 5-HT uptake inhibitors are not abused (Lichtigfeld and Gillman 1998), and the reinforcing potency of amphetamine analogues was negatively correlated with affinity for the 5-HT transporter (Wee et al. 2005; Ritz and Kuhar 1989). Increasing synaptic 5-HT by addition of the releasing stimulant, fenfluramine, decreased amphetamine self-administration by primates (Wee and Woolverton 2006) supporting not only the idea that 5-HT releasing stimulants are not reinforcing but also that non-selective activation of 5-HT receptors is inhibitory to psychostimulant-produced reward (Rothman and Baumann 2006).

Evidence has accumulated that the 5-HT response does indeed limit the reinforcing effects of MDMA. Self-administration by rats proceeds more slowly than self-administration of other amphetamine-type stimulants, and a relatively large percentage of rats fail to acquire MDMA self-administration (Schenk et al. 2007). We wondered whether this reflected differences in the effect of MDMA on 5-HT and reasoned that rats that were most responsive to this neurochemical effect might be less likely to self-administer MDMA. This hypothesis was supported. MDMA-produced increases in synaptic 5-HT, as measured by in vivo microdialysis, predicted whether rats would learn to self-administer MDMA or not (Bradbury et al. 2014); rats that failed to acquire self-administration were more responsive to the MDMA-produced increase in 5-HT. Acquisition of self-administration by laboratory rats was facilitated by a neurotoxic, 5,7 DHT lesion (Bradbury et al. 2014)

or by a mutation that prevented functioning of the 5-HT transporter (Oakly et al. 2014). These converging lines of evidence support the idea that 5-HT is inhibitory to MDMA self-administration.

The large increase in synaptic 5-HT, relative to DA, produced following administration of MDMA would, therefore, be expected to limit the development of an SUD. Several studies that applied DSM lV criteria, however, provided convincing evidence of MDMA dependence (Smith et al. 2014; Cottler et al. 2001; Degenhardt et al. 2010; Topp et al. 1999; Yen and Hsu 2007; McKetin et al. 2014). The DSM V no longer considers drug dependence but, instead, recognizes SUDs resulting from the use of 10 separate classes of drugs. MDMA is not amongst those drugs that are specifically acknowledged in the DSM, but use can, nonetheless, produce many of the symptoms that the DSM includes in the diagnosis of an SUD. Of the 11 symptoms that are used to define an SUD, at least 5 apply to some users of MDMA. For example, some users reported (1) taking the substance in larger amounts or for longer than they meant to (Soar et al. 2006; Parrott 2013), (2) cravings and urges to use the substance (Davis and Rosenberg 2014; Hopper et al. 2006; Huxster et al. 2006), (3) continuing to use, even when they knew they had a physical or psychological problem that could have been caused or made worse by the substance (Cottler et al. 2001, 2009; Yen and Hsu 2007), (4) tolerance to the positive effects (Yen and Hsu 2007; Parrott 2005; Kirkpatrick et al. 2014; Peroutka et al. 1988) and (5) development of withdrawal symptoms (McKetin et al. 2014; Peroutka et al. 1988; Curran and Travill 1997). The potential to develop an SUD is somewhat of a puzzle given the pharmacology of MDMA. Our thesis is that repeated exposure to MDMA renders the drug more comparable to stimulant drugs and that this change is required for the development of an MDMA SUD.

The human literature supports this idea. In experienced users, MDMA produced subjective effects that overlapped with those of both the 5-HT releasing stimulant, mCPP, and amphetamine (Tancer and Johanson 2001, 2003). The reinforcing effects, however, were only observed following administration of MDMA and amphetamine; mCPP did not produce positive effects, supporting the idea that stimulated 5-HT does not mediate the positive effects of MDMA. This idea was further reinforced by the demonstration that the dopamine antagonist, haloperidol, but not the 5-HT antagonist, ketanserin, blocked the positive mood produced following MDMA administration to healthy individuals with virtually no previous MDMA use as well as in experienced users (Liechti and Vollenweider 2000; Liechti et al. 2000). Some experienced users had difficulty differentiating the subjective effects of amphetamine and MDMA (Johanson et al. 2006) or methamphetamine and MDMA (Kirkpatrick et al. 2012), and MDMA administered to experienced users produced positive effects that were comparable to effects produced by other amphetamines (Kirkpatrick et al. 2012).

Because these studies in humans are almost always carried out in experienced users, there is limited information on whether the subjective effects change as a function of repeated drug use. This might be important because repeated exposure to various amphetamine-type drugs can markedly alter the pharmacodynamic responses, with some responses becoming sensitized and others becoming

desensitized. Indeed, there is ample evidence of neuroplasticity derived from preclinical studies of the effects of repeated exposure to psychostimulant drugs, including MDMA. We propose that there are persistent alterations in the pharmacodynamic profile due to both 5-HT and DA neuroplasticity and that these changes underlie the development of an MDMA SUD.

An obvious prerequisite for the development of any SUD is drug exposure. How much drug exposure and the required conditions of the exposure are still unknown. It has become clear, however, that repeated intermittent exposure to psychostimulants often initiates a cascade of neurochemical events that renders some users susceptible to an SUD. The increase in synaptic DA, particularly in the nucleus accumbens shell, is a crucial initial response for coding the rewarding effect of a drug and enabling the development of associative learning that is critical for drug-seeking expressed in response to stimuli or contexts associated with the rewarding effect of a drug. Following repeated, intermittent exposure to most psychostimulant drugs, this DA response becomes sensitized (Robinson and Becker 1986) and this sensitized response might underlie the preferential attention to drugs of abuse over other, natural, reinforcers.

The nucleus accumbens also receives glutamatergic input from the prefrontal cortex and amygdala (Voorn et al. 2004). Thus, there are converging DA and glutamatergic inputs in the nucleus accumbens that modulates the response to psychostimulant drugs. Increased drug-produced DA in hippocampus and amygdala also strengthens the relationship between a response and the delivery of the drug reinforcer, i.e. learning stimulus–reward associations. Additionally, midbrain DA neurons project to cortical sites, and pyramidal neurons of the mPFC send glutamatergic projections to the ventral tegmental area, the nucleus accumbens and the amygdala (Gabbott et al. 2005; Hoover and Vertes 2007), further modulating those neurochemical responses. Increased DA in prefrontal, anterior cingulate and orbitofrontal regions impacts cognitive control and executive functioning via modulation of glutamatergic outputs to limbic regions.

Following repeated, intermittent exposure to many psychostimulant drugs, a number of neuroadaptations occur that are relevant to the preferential attendance to drugs and drug-related stimuli and the loss of inhibitory control regarding drug-seeking in response to those stimuli. The impact of cue presentation on drug-seeking might reflect, at least in part, a shift in the stimulus that elicits the DA response from the drug to anticipation of the drug effect (Schultz 1997). This suggests a strengthening of signals that mediate conditioned reinforcement and a corresponding decrease in the strength of the signal that mediates primary drug reinforcement at the level of the ventral striatum. At the same time, there is an inability to inhibit the behaviour that will result in drug-taking, suggesting a decrease in executive functioning and control at the level of the prefrontal, orbitofrontal and anterior cingulate cortices.

Some studies from our laboratory have confirmed the important role of the continued presentation of a stimulus associated with self-administered infusions in drug-taking behaviour. Rats were trained to self-administer cocaine (Schenk and Partridge 2001) or MDMA (Daniela et al. 2006), and each self-administered

infusion was paired with the illumination of a stimulus light. Following extensive experience, drug infusions delivered contingent on an operant response, but without the associated light stimulus were relatively ineffective in maintaining operant responding. Importantly, the light stimulus acquired conditioned reinforcing properties that maintained responding in the absence of the drug reinforcer, suggesting a shift from drug-maintained responding to stimulus-maintained responding. Responding under a second-order schedule also demonstrates the high rate of responding that is maintained when only a drug-associated stimulus is presented (Schindler et al. 2002; Everitt and Robbins 2000).

Additionally, a large number of studies have documented the ability of drug-associated stimuli to elicit craving in abusers (Childress et al. 1993; Jasinska et al. 2014) and drug-seeking in some animal models (Crombag et al. 2008; Marchant et al. 2014; Grimm et al. 2001; Tzschentke 1998). Alterations in prefrontal cortical glutamatergic outputs to the nucleus accumbens (Kalivas 2009) and other downstream outputs that might include increased activation of dorsal striatal circuitry (Everitt and Robbins 2005, 2013) are posited to be of particular relevance to persistent drug-seeking behaviour in response to exposure to these drug-associated stimuli. These glutamatergic outputs are modulated by a large number of neurochemical systems including GABA, DA and 5-HT (Volkow and Baler 2014).

MDMA, like other psychostimulant drugs of abuse, increased DA preferentially in the nucleus accumbens shell (Cadoni et al. 2005). Both the human (Liechti and Vollenweider 2000) and animal (Brennan et al. 2009) literature support the idea that the MDMA-produced increase in DA is important for the reinforcing effects. Effects of repeated exposure on brain DA are, however, inconsistent. There was no change in DA transporter density in ecstasy users (Reneman et al. 2002; McCann et al. 2008), but one study suggested increased DOPA uptake in former ecstasy users (Tai et al. 2011). Ecstasy, polydrug, users were less sensitive to some effects of the D2 agonist, bromocriptine (Gerra et al. 2003), suggesting downregulated DA D2 receptor mechanisms. Results of preclinical studies are also equivocal. Some preclinical studies have failed to observe MDMA-produced changes in DA neurochemistry following repeated exposure (Shortall et al. 2013; Reveron et al. 2010; Fantegrossi et al. 2004; Shankaran and Gudelsky 1999; Baumann et al. 2008), and others have shown an increase (Shortall et al. 2013; Ludwig et al. 2008; Kalivas et al. 1998; Colussi-Mas et al. 2010).

In contrast to these neurochemical studies, a large number of behavioural studies have suggested that repeated MDMA exposure sensitized DA substrates. Acute exposure to MDMA produces hyperactivity that became sensitized following repeated exposure (Modi et al. 2006; Yang et al. 2011; Bradbury et al. 2012; Colussi-Mas and Schenk 2008; Schenk and Bradbury 2015; Ball et al. 2009, 2010, 2011) even in SERT knock out rats (Lizarraga et al. 2014). The locomotor-activating effects of MDMA have been shown to be dependent upon DA activation (Gold et al. 1989; Bubar et al. 2004; Daniela et al. 2004), although 5-HT mechanisms have also been demonstrated, especially in hyperactivity produced following administration of (+) MDMA (Callaway et al. 1990; Bankson and Cunningham 2002; McCreary et al. 1999). Additionally, some studies have shown

cross-sensitization between the behavioural effects of MDMA and other psychostimulant drugs (Bradbury et al. 2012; Moreno-Sanz et al. 2009; Fletcher et al. 2001; Schenk et al. 2003). Importantly, drug-seeking following extensive MDMA self-administration was produced by DA, but not 5-HT agonists, and was attenuated by DA antagonists (Carati and Schenk 2011). Thus, although there is limited direct evidence of effects of repeated MDMA exposure on DA neurochemistry, the behavioural data are consistent with sensitized dopamine responses. A question remains as to whether this sensitized behavioural response reflects direct effects on DA neurotransmission or indirect effects resulting from other MDMA-produced neuroadaptations.

There is substantial evidence of alterations in 5-HT neurochemistry following repeated exposure to MDMA. Acute exposure to MDMA produces marked increases in synaptic 5-HT activating 5-HT receptors in a non-selective manner. Following repeated exposure to MDMA, there are many indices of compromised 5-HT neurotransmission. In particular, density of SERT is decreased in ecstasy users (Parrott 2013; McCann et al. 2008; Benningfield and Cowan 2013; Di Iorio et al. 2012; Parrott et al 2014; McCann et al. 2000) (but see (Cowan 2007) for a review of earlier human neuroimaging studies) and in rats and non-human primates (Schenk et al. 2007; Biezonski and Meyer 2011; Capela et al. 2009; Cole and Sumnall 2003; Ricaurte et al. 2000) that were exposed to MDMA. This decrease might produce additional alterations in receptor mechanisms that directly mediate the development of an SUD.

'Those who may have predicted that molecular biology would largely simplify the life of pharmacologists have missed the point for 5-HT research' (Hoyer et al. 2002). There are at least 14 different 5-HT receptor subtypes in 7 families of receptors (5-$HT_{1\text{-}7}$). Some of these receptors are localized on DA-containing nerve cell bodies and terminals or on cell bodies and terminals of neurons that modulate DA responses (Alex and Pehek 2007). For example, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} have been localized to the ventral tegmental area (Doherty and Pickel 2000), nucleus accumbens (Mengod et al. 1990) and prefrontal cortex (Mengod et al. 1990; Pazos and Palacios 1985). They are, therefore, well positioned to impact DA neurotransmission directly or to modify the impact of other brain systems on DA (Di Giovanni et al. 2010; Esposito et al. 2008). Some are also of interest because they are highly localized to prefrontal cortical substrates, activation alters glutamate signalling in the prefrontal cortex, and activation also impacts some measures of impulsivity/compulsivity (Homberg 2012; Clark et al. 2004). MDMA decreased glutamate-stimulated firing of nucleus accumbens cells (White et al. 1994; Obradovic et al. 1996). One study has demonstrated hypofrontality in MDMA abusers (Bosch et al. 2013) that might reflect the decreased SERT binding and ensuing altered 5-HT receptor mechanisms.

Reductions in SERT following repeated MDMA were accompanied by increased 5-HT_{2a} receptor binding (Benningfield and Cowan 2013; Urban et al. 2012). It appears likely that the increase in 5-HT_{2a} receptors is secondary to the decrease in SERT since chronic 5-HT depletion induced by tryptophan depletion in rats (Cahir et al. 2007) or neurotoxic 5,7 DHT lesions to mice (Heal et al. 1985) also

increased 5-HT_{2a} receptor binding. This receptor is densely localized on PFC pyramidal neurons, and activation regulates glutamate release (Aznar and Klein 2013). It is possible that the effects of upregulated 5-HT2a receptor mechanisms on impulse control might relate to compulsive drug-seeking consistent with an MDMA SUD.

A number of preclinical models have been developed to investigate impulsive behaviour in animals (Pattij and Vanderschuren 2008), but the most widely used with respect to drug addiction are measures of behavioural inhibition, such as the 5-choice serial-reaction time task (5CSRTT), and measures of choice preference for a delayed reward, such as the delay-discounting paradigm. These measures show good validity as they are variants of those used to assess aspects of impulsive behaviour in humans (Robbins 2002; Evenden 1999).

Measures of behavioural inhibition model 'response impulsivity'. An animal is typically required to perform an operant in order to receive a reinforcer, but this operant must be performed after some delay. Operant responses that are made before the appropriate time are an index of response impulsivity. Most measures of response impulsivity employ a variation of a reaction time task. Reaction time tasks require an animal to maintain some response (e.g. hold down a lever) until a stimulus (light, tone) indicates that ceasing the response will produce a food reward (Blokland 1998). Impulsivity is operationalized as premature cessation of the required response. The 5CSRTT is the most widely used reaction time task and the most studied measure of response impulsivity in drug addiction. In this task, an animal is required to wait for a light stimulus to appear in one of five apertures before performing a nosepoke in that aperture. A nosepoke in an aperture before the light stimulus is presented is a premature response and indicates response impulsivity (Robbins 2002). The time between presentation of light stimuli (the intertrial interval, ITI) can be varied, with longer ITIs producing more premature responses.

Measures of choice preference for a delayed reward model 'decision impulsivity'. In the delay-discounting paradigm, an animal is required to choose between a small, immediate reinforcer and a larger, but delayed, reinforcer. At short delays, there is a preference for the large reinforcer, but as the delay for the larger reinforcer is increased, a preference for the immediate reinforcement develops. The delay following which there is no longer a preference for the larger, delayed reinforcer, indicated by a 50 % chance of choosing either the small or large reward, is defined as the 'indifference point'. Lower indifference points, showing intolerance to delay, are indicative of greater impulsivity. Indifference points for various delays can be obtained, and an indifference curve can be generated, by plotting the indifference point against delay, with a faster rate of decay reflecting greater impulsivity (Evenden 1999).

Delay discounting and reaction time tasks can be used to determine impulsivity scores across a group of animal subjects, which can then be divided into 'low impulsive' (LI) groups and 'high impulsive' (HI) groups. HI subjects are usually defined as those in the upper quartile of impulsivity scores, with LI subjects being those with impulsivity scores in the bottom quartile. These two groups can then be compared to see the impact of impulsivity on drug self-administration.

A role of 5-HT_{2a} receptors in both measures of impulsivity has been demonstrated. Systemic administration of the 5-$HT_{2a/2c}$ agonist, 2,5-Dimethoxy-4-iodoamphetamine (DOI), increased premature responding on the 5CSRTT (Koskinen and Sirviö 2001; Koskinen et al. 2003), and this effect was blocked by the 5-HT_{2a} antagonist, ketanserin (Koskinen et al. 2000a, b), suggesting a 5-HT_{2a} effect. DOI administration also increased impulsive behaviour in the choice reaction time task (Blokland et al. 2005) and increased preference for the small, immediate reinforcer in the delay-discounting paradigm (Evenden and Ryan 1999), indicating greater impulsivity. Furthermore, blockade of 5-HT_{2a} receptors decreased impulsive responses. The 5-HT_{2a} antagonists, ketanserin (Passetti et al. 2003; Talpos et al. 2006; Fletcher et al. 2007; Ruotsalainen et al. 1997) and M100907, (Fletcher et al. 2007; Winstanley et al. 2004) decreased premature responses on the 5CSRTT, or the similar 1CSRTT (Anastasio et al. 2011). HI rats, defined by performance on the 1CSRTT, showed a greater behavioural response to DOI and showed greater 5-HT_{2a} receptor binding in the frontal cortex (Fink et al. 2015). Finally, premature responses were correlated with 5-HT_{2a} protein levels (Anastasio et al. 2015). These findings illustrate a likely role of 5-HT_{2a} receptor activation in impulsive behaviour, but are unfortunately limited by the lack of selective pharmacological tools, particularly agonists, targeting 5-HT_{2a} receptors. As more selective ligands are produced, the specific role of 5-HT_{2a} receptor activation on impulsive behaviour will be able to be further elucidated.

Based on these findings, an increase in 5-HT_{2a} receptors associated with MDMA exposure could increase impulsivity, thereby increasing compulsive drug-taking consistent with an SUD. The role of impulsivity in different aspects of drug self-administration in animals has been determined, but most research has focused on drugs other than MDMA. Some studies have looked at the acquisition and maintenance of self-administration, based on the idea that HI subjects might be more prone to take drugs (Perry and Carroll 2008). When impulsivity was determined using a delay discounting task, HI rats consumed more ethanol (Poulos et al. 1995), or cocaine (Perry et al. 2005, 2008; Koffarnus and Woods 2013) and cocaine self-administration were acquired more quickly and in a higher percentage of HI rats (Perry et al. 2005; Zlebnik and Carroll 2015). Impulsivity measured by performance in the 5CSRTT did not, however, predict acquisition of cocaine self-administration (Belin et al. 2008; Dalley et al. 2007). This difference might reflect different mechanisms for the two forms of impulsivity. On the other hand, rats that were HI as measured by 5CSRRT performance acquired nicotine self-administration more readily (Diergaarde et al. 2008), and a strain of mice with high impulsivity showed enhanced ethanol self-administration (Loos et al. 2013). Following acquisition, HI rats self-administered more cocaine per hour than LI rats and exhibited an upward shift in the cocaine dose–response curve (Dalley et al. 2007).

The reinstatement of drug-seeking after abstinence or extinction is an animal model of relapse that has also been associated with impulsivity (Perry and Carroll 2008; Cunningham and Anastasio 2014). Reinstatement of cocaine seeking was greater in HI rats when characterized by either the 5CSRTT (Economidou et al.

2009), or a delay discounting task (Perry et al. 2008), and one study found that HI rats met more DSM-IV-like criteria for cocaine dependence (Belin et al. 2008). HI rats, when defined by delay discounting, showed greater reinstatement of nicotine seeking than LI rats, and when impulsivity was defined by the 5CSRTT, HI rats showed greater resistance to extinction (Diergaarde et al. 2008). Furthermore, HI rats were less responsive than LI rats to pharmacological treatment to reduce cocaine seeking (Regier et al. 2014). Along with greater ethanol consumption and seeking, alcohol preferring 'P' rats show greater delay discounting (Beckwith and Czachowski 2014), while the highly impulsive BXD15 mice showed greater reinstatement of ethanol seeking (Loos et al. 2013).

To our knowledge, only one study has assessed the role of impulsivity on MDMA self-administration. Impulsivity as determined by the 5CSRTT did not predict the latency to acquire MDMA self-administration in rats, but it predicted the magnitude of the drug-seeking response for MDMA (Bird and Schenk 2013). In so far as drug-seeking is a correlate of propensity to relapse following abstinence, this finding suggests that impulsivity can be directly linked to an MDMA SUD.

In drug users, impulsivity is a risk factor for initiating drug-taking, for escalating drug use and for developing SUDs (Perry and Carroll 2008; De Wit 2009). For example, impulsive traits in youth and young adulthood positively predicted future drug use, an earlier onset of drug-taking, and the likelihood of developing an SUD (De Wit 2009; Sher et al. 2000; Tarter et al. 2007; Kirisci et al. 2007). The noted upregulation of 5-HT_{2a} receptors in MDMA users could be expected to contribute to impulsive decision-making. Indeed, there is some evidence that ecstasy users show heightened levels of impulsivity compared to non-ecstasy controls (Morgan 1998), but whether this abnormal level of 5-HT_{2a} receptors is a cause, or an effect, of MDMA use remains to be determined.

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