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Recreational MDMA (3,4-methylenedioxymethamphetamine; 'Ecstasy'): current perspective and future research prospects.

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Abstract.

Aims: to debate current understandings about the psychobiological effects of recreational MDMA or 'ecstasy', and recommend theoretically-driven topics for future research.
Methods: recent empirical findings, especially those from novel topic areas were reviewed. Potential causes for the high variance often found in group findings were also examined.
Results and conclusions: the first empirical reports into psychobiological and psychiatric aspects from the early 1990s concluded that regular users demonstrated some selective psychobiological deficits, for instance worse declarative memory, or heightened depression. More recent research has covered a far wider range of psychobiological functions, and deficits have emerged in aspects of vision, higher cognitive skill, neurohormonal functioning, and foetal developmental outcomes. However, variance levels are often high, indicating that while some recreational users develop problems, others are less affected. Potential reasons for this high variance are debated. An explanatory model based on multi-factorial causation is then proposed.
Future directions: a number of theoretically driven research topics are suggested, in order to empirically investigate the potential causes for these diverse psychobiological deficits. Future neuroimaging studies should study the practical implications of any serotonergic and/or neurohormonal changes, using a wide range of functional measures.

Key words: MDMA - Ecstasy - CNS - stimulant –memory – cognition - psychobiology

Introduction.

The recreational use of 3,4-methylenedioxymethamphetamine (MDMA) commenced primarily during the mid-1980s, and the first empirical reports on its physiological, psychobiological, and psychiatric aspects were published within a few years (Shulgin, 1986; Peroutka, 1989; McCann and Ricaurte, 1991). These were complemented by early cohort studies (Peroutka et al, 1988; Solowij et al, 1990; Krystal et al, 1992), and since then numerous empirical investigations have been conducted. The emergent findings have been the focus for a number of reviews (McCann and Ricaurte, 2000; 2014; Parrott, 2001, 2006, 2013a; Rogers et al, 2009; White 2014). These reviews have shown that recreational users can display a range of psychobiological deficits, while other psychobiological functions may remain intact. The first areas of deficit to be described included aspects of memory and cognition, sleep, and certain psychiatric disorders such as depression (McCann and Ricaurte, 1991; Curran and Travill, 1997; Schifano et al, 1998; Parrott et al, 1998; McGuire, 2000; Wareing, et al, 2000; Verkes, et al., 2001; Soar et al, 2001; McCardle et al, 2004). Subsequent research investigated a wider range of psychobiological functions, and several further areas of deficits have been identified. They have included vision, higher cognition, psychomotor performance, neurohormonal activity, immunocompetance, and its effects when taken by pregnant women on birth outcomes and subsequent child development (Gerra et al, 2003; Fisk, et al., 2005; Murray et al, 2012; Parrott, 2013b; Singer et al, 2012a,b, 2016). One aim of this current perspective paper is to summarise the wider range of problems revealed by this expansion in research.

As with many of the earlier studies into the psychobiological effects of MDMA consumption, these more recent investigations have described an intriguing mixture of significant and non-significant findings. This is certainly apparent in neurocognition research, particularly in the area of executive functioning. While some studies report ecstasy-related cognitive dysfunctions, other studies report intact task performance (Murphy et al, 2009; Roberts et al, 2016a). Furthermore, even when a single cognitive measure is used, deficits are apparent

in some studies - but not in others (Rogers et al, 2009). This variation also occurs with vision research, since while some visual skills remain unaffected, other visual tasks demonstrate significant impairments (Murray et al, 2012). Similarly with sleep studies, some individuals report impairments - whereas others do not (McCann et al, 2007, 2009; Ogeil et al, 2011, 2013). In neurohormonal research, while overall group cortisol levels are significantly raised, the MDMA subgroup data often shows pronounced variance, which again indicates considerable variation in drug effects between individuals (see Figure 1 in Parrott et al, 2014). It is important that this variance in physical and psychological findings is incorporated into our models of causation. Hence, this current perspective will debate the factors which may influence the development *or non-development* of neuropsychobiological problems in recreational Ecstasy/MDMA users. It will also suggest some future research topics with a theoretical rationale for examining the causes of this variation.

Neurocognition

The first area of psychobiological deficit to be associated with MDMA usage was declarative memory (Krystal et al, 1993). Many subsequent studies have empirically confirmed the presence of memory deficits in some Ecstasy/MDMA users, although as noted earlier, a degree of variation has also been apparent (Laws and Kokkalis, 2007; Rogers et al, 2009). Many studies have also observed that prospective memory is impaired in MDMA users; with damage to 5-HT rich areas in the hippocampal and frontal processing areas being suggested as a potential mechanism for these impairments (Heffernan et al, 2001; Rendell et al, 2007; Hadjiefthyvoulou et al, 2011a,b; Parrott, 2013b). MDMA is a selective serotonin neurotoxin in laboratory animals, and neuroimaging studies have found reduced SERT levels in humans, although there is active debate over the underlying nature of these serotonergic changes (Kish et al, 2010; Di Iorio et al, 2012; Benningfield and Cowan, 2013; Parrott, 2013b). In this context, Quelch et al (2012) is particularly relevant for debating how to interpret the many SERT imaging studies which have used the ligand DASB.

Given the reductions in SERT density in the cerebral cortex, it would be expected that the neurocognitive functions subserved by these 5-HT rich areas should also show a decline. Areas of the dorsolateral prefrontal cortex are densely innervated by 5-HT neurons, and are understood to belie executive functioning ability (Curtis and D'Esposito, 2003). Many studies have investigated executive functioning in ecstasy/MDMA users, although again the performance findings have been quite varied (Murphy et al, 2009). One potential reason for this inconsistency may be that the tasks used in these earlier studies were not function specific. Miyake et al (2000) proposed that overall executive functioning comprised three correlated, but distinct, sub-functions: *updating*, *switching*, and *inhibitory control*, while a fourth subcomponent of *access* to semantic/long term memory was added by Fisk and Sharp (2004). In a systematic review and meta-analysis of executive performance in ecstasy users versus polydrug controls, it was concluded that ecstasy users showed performance deficits in updating, switching and access, but not in inhibitory control (Roberts et al., 2016b). This is particularly interesting, given that a more recent theoretical framework of executive functioning suggested that inhibitory control might not be an independent factor (Miyake et al, 2012). Mention should also be made of Halpern et al (2011), since this study has often been cited as finding no cognitive deficits in Ecstasy/MDMA users. Indeed their Abstract suggested only slight deficits: 'We found little evidence of decreased cognitive performance in ecstasy users, save for poorer strategic self-regulation', althought they also noted: 'This finding contrasts with many previous findings including our own', However close examination shows that there were significant performance deficits on several cognitive

measures; these were debated in the following commentaries (Fisk et al, 2011; Parrott, 2011; Rodgers et al, 2011).

Recent neuroimaging studies have increased our understanding of how MDMA may alter cognitive function. Using function specific tasks, Roberts and Montgomery (2015a,b) observed changes in neuronal activation in Ecstasy/MDMA users compared to non-users, whilst completing tasks that tap access and inhibitory control. In each case, the findings suggested that ecstasy users were engaged in more effortful cognition, indexed by increases in oxygenated haemoglobin, to those brain sites needed for cognitive performance. It is proposed that this extra effort allowed them to reach the performance levels achieved by the controls. The authors concluded that these changes in haemodynamics may reflect serotonergic neuroadaptation from repeated Ecstasy/MDMA use. These findings also highlighted the greater sensitivity of neuroimaging measures for detecting cognitive changes, when compared to behavioural measures alone. These studies were conducted using functional near-infrared spectroscopy (fNIRS). This is a relatively low cost neuroimaging technique, which measures changes in oxygenated and deoxygenated haemoglobin within the pre-frontal cortex. It measures near-infrared light at two wavelengths, one of which is attenuated by oxygenated haemoglobin, while the other is attenuated by deoxygenated haemoglobin. This can measure changes in haemodynamics to areas of the pre frontal cortex involved in many higher order cognitive tasks. This imaging technique is also robust to movement artefacts, so that it can be used with cognitive tasks requiring vocalisations or limb movements. The utility of fNIRS for future research has recently increased with whole head fNIRS systems, especially since they can be used simultaneously with EEG for multi-modal neural signalling. This may enable future research to elucidate MDMA effects on brain haemodynamics and electrophysiology, in relation to a wide range of cognitive functions. The contributory role of the serotonin system should also be monitored, since it displays modulatory effects for many different aspects of neurocognition (Meneses, 1999; Schmitt et al, 2006; Švob-Štrac et al, 2016)

Vision.

The visual cortex also receives serotonergic input from the raphe nuclei, and due the long axon distances, it appears to be particularly vulnerable to ecstasy-mediated alterations (Roberts et al. 2016a). In a series of studies utilising responses to visual illusions, impairments in some aspects of visual processing have been demonstrated among abstinent ecstasy consumers. For instance, they have demonstrated compromised orientation processing of stimuli at the level of the primary visual cortex or V1 (Dickson et al, 2009). These visual changes were positively correlated with the frequency and quantity of ecstasy use, but were independent of other drugs consumed. Subsequent studies from another laboratory have replicated this impairment, and demonstrated that the underlying mechanism may reflect a serotonergic role in lateral inhibitory processes in orientation sensitive neurons (White et al, 2013). However, such orientation processing deficits are not apparent in response to stimuli primarily processed in prestriate cortex V2 (Murray et al, 2012); this may possibly arise from the pooling of orientation signals as the information is being processed at higher levels of the visual cortex.

Using apparent global motion paradigms, Hall (2010) demonstrated pronounced motion processing deficits, as indicted by higher global motion thresholds; these visual deficits were related to Ecstasy/MDMA consumption, but were independent of other drugs including cannabis. Complex motion processing deficits among abstinent ecstasy consumers have also been identified by others (Rizzo et al, 2005). This work directly contradicts another small

scale study using a similar paradigm that has suggested improved motion processing - albeit only in a subset of consumers (White et al, 2014). These effects on basic visual functioning have the potential to contribute to impairments in daily activities reliant on these processes, such as driving. In acute dosing studies, MDMA has been observed to impair various aspects of driving ability, including overall driving performance, and signalling adherence (Stough et al, 2012); these studies need to be repeated with chronic users. Furthermore it also changes other aspects of ocular activity, with increasing nystagmus (Downey et al, 2012), and driving problems such as tailgating are more apparent in abstinent Ecstasy/MDMA consumers (Dastrup et al, 2010). Recent studies in our laboratory have failed to identify any deficits among abstinent ecstasy consumers on motion processing tasks in the context of simulated driving, such as estimation of time to collision with oncoming traffic (Bernard, 2011). This suggests that any impairment in coarse behavioural tasks such as driving, may not simply be a reflection of impaired visual processing. For instance, heightened levels of impulsivity have also been found, and this may be a contributing factor (Quednow et al, 2007). There may also be some differences in visual scanning of the overall driving environment. Alterations in visual perception and attention as indicated by saccadic eye movement patterns may provide an indicator of how changes in visual scanning behaviour contribute to an increase in the risk of accidents in abstinent MDMA users. Future research concerning the on-road and simulated driving ability of Ecstasy/MDMA users, both on drug and drug free, could benefit from inclusion of saccadic eye movement technology to provide an index of more basic visual abilities and their putative disruption.

Polydrug factors.

Recreational Ecstasy/MDMA users often take a range of other psychoactive drugs, so an important issue is the neuropsychological consequences of this polydrug usage. In order to partially address this factor, most studies employ a comparison group of polydrug users who have taken other illicit recreational drugs, but not Ecstasy/MDMA (Fox et al, 2001; Fisk et al, 2005; Singer et al, 2016). Some studies employ two comparison groups: polydrug/illicit drug users, and legal drug-users (Hadjiefthyvoulou, et al, 2011a; Roberts and Montgomery, 2016b), while others have employed multiple comparison groups. For instance, Parrott et al (2001) compared 768 young volunteers divided into six subgroups: non-users of any psychoactive drug (n=150); alcohol and/or tobacco (n=185); cannabis and alcohol/nicotine (n=97); non-MDMA polydrug (n=102); light Ecstasy/MDMA polydrug (n=115); and heavy Ecstasy/MDMA polydrug users (n=119). Self-rated psychiatric problems increased in line with greater psychoactive drug usage. The large sample sizes also facilitated the attribution of specific problems to particular drugs, with the Ecstasy/MDMA findings outlined in Milani et al (2000). Taurah et al (2013) assessed 997 participants divided into six subgroups: no psychoactive drugs (n=182); alcohol and nicotine (n=172); cannabis, alcohol and nicotine (n=163) ; non-MDMA polydrug (n=169); current MDMA polydrug (n=154); and *former* MDMA polydrug (n=157). They found significant impairments in both subgroups of Ecstasy/MDMA polydrug users across the whole of their test battery - which covered four psychobiological functions (sleep, impulsiveness, depression, and memory). The former Ecstasy/MDMA users showed minimal signs of functional recovery, despite nearly 5-years of abstinence. The large sample size also allowed the psychobiological effects of other drugs to be both analysed by regression, and statistically controlled via covariance. Taurah et al (2013) found that alcohol, cannabis, cocaine and ketamine were each associated with some psychobiological deficits, with moderate-to-high beta values. Furthermore, when alcohol, amphetamine, cannabis, cocaine, heroin, and ketamine were entered as co-variants, the deficits attributable to Ecstasy/MDMA remained significant - in both the current and former users.

Some studies have compared low and high Ecstasy/MDMA user subgroups, while others have statistically investigated the associations between specific performance deficits and individual drugs, in order to investigate this polydrug factor (Fox et al, 2001; Rodgers et al, 2003). None of these approaches are however ideal, since the heavier Ecstasy/MDMA users are often more experienced users of other drugs (see Table 1 in Parrott et al, 2001). Hence despite the employment of polydrug users as controls, and statistical procedures such as regression and covariance, none of the current approaches provide a full solution. In methodological terms, recreational drugs research will always be quasi-experimental. Laboratory animal research can be relevant and useful, since it allows full empirical control, with placebo conditions and random drug allocation. Meta-analyses and theoretical debates around 'construct validity' are also crucial for our critical awareness and conceptual understanding (Parrott, 1991, 2013b; Laws and Kokkalis, 2007; Rogers et al, 2009). It should be noted that Ecstasy/MDMA research has been at the forefront of this complex issue. It was noted in most of the early reviews, and an early theoretical debate (Parrott, 2004), had been followed by a more extensive and comprehensive review (Mohamed et al, 2011). Nearly every paper in this field currently refers to Ecstasy/MDMA 'polydrug' users. This is far less apparent in other fields of recreational drug research, such as cannabis, nicotine, cocaine or amphetamine (Parrott, 2015). Hence multiple-drug-usage remains a pervasive problem across the whole field of recreational drugs research. For the future, more creative and sophisticated solutions need to be devised, perhaps incorporating molecular imaging, pharmacological challenges and genetic research methodologies, and well designed prospective studies.

Human pregnancy and foetal aspects

Psychoactive drugs can impair foetal development, and deficits have been found with alcohol, cocaine, nicotine, heroin, cannabis, and many other drugs (Minnes et al, 2011; Behnke et al, 2013). The devastating effects of methyl mercury poisoning in the 1950s, and thalidomide in the 1960s, showed the profound foetal vulnerability to all toxins - even at low or negligible doses. Hence it is important to empirically investigate the neurobehavioral effects of prenatal Ecstasy/MDMA exposure on infant development. The pharmacodynamic effects of acute Ecstasy include changes to the 5-HT system, the HPA axis and gonadal hormones (Dickerson et al., 2008; Parrott et al., 2014), and all these factors may be linked to reductions in prenatal growth and postnatal development (Davis et al, 2011, Boukhris et al, 2016). The neuroadaptations with MDMA have also been associated with fluctuations in mood, cognition, sleep, and appetite (Curran and Travill, 1997; Parrott, 2002), additional factors which may also impact on foetal development (Okun et al, 2013, Kinsella and Monk, 2009). In recent years, women of child-bearing age have been consuming drugs such as Ecstasy to similar extents as men (Degenhardt et al, 2008), setting them at a sex-specific disadvantage for secondary risk factors such as psychiatric co-morbidity (Fox and Sinha, 2009).

The DAISY study recruited women who used Ecstasy and/or other recreational drugs at any time during their pregnancy, and prospectively assessed the neuropsychological development of their infants at various time points post-partum (Singer et al, 2012a,b, 2016). The pregnant women were categorised into three groups dependent upon their Ecstasy/MDMA usage during pregnancy: heavy Ecstasy users (n=13; 1.7 ± 1.8 tablets per week), light Ecstasy users (n=12; 0.09 ± 0.06 tablets per week), and polydrug user controls (n=68). The groups were statistically matched for a range of salient individual, drug and

environmental factors. The Ecstasy/MDMA using mothers had used more cannabis, so this was employed as a co-variate. These women were predominantly from middle class backgrounds, living with partners, receiving similar annual incomes, similarly educated and showed no variation in terms of psychological profiles, or drug dependence.

Physical differences in foetal development were not observed, although at 1 month the Ecstasy-exposed infants were somewhat more lethargic and less hypertonic. At 4 months, the heavily Ecstasy-exposed infants performed significantly worse on gross motor skills as measured by the Alberta Infant Motor Scale (Piper et al, 1992), and Bayley Behavioral Rating Scales (Bayley, 1993). At 12 months post-partum these psychomotor decrements were again more severe in the heavily-exposed Ecstasy group compare to controls, and they persisted at two years of age, when the study ended (Singer et al, 2016). The lightly exposed Ecstasy babies were not impaired at any time point, although their very low levels of maternal Ecstasy exposure should be noted. One of the babies in the heavy exposure group showed severe birth defects, consistent with earlier case study reports of birth defects in MDMA exposed infants (McElhatton et al, 1999). These decrements in motor development may impact on later social relationships, thinking, and language. Gross motor development allows infants to explore their environment, while fine motor skills represent the beginnings of object-based play and tool use which facilitate pre-verbal communication. Consequently, while language-related deficits were not observed in the DAISY study, social communication and interpersonal issues may possibly arise at later developmental stages (Chaibal et al, 2016). In terms of future research, our main recommendation is for an extended and prolonged replication. It would assess a larger numbers of ecstasy/MDMA exposed women, with the infants tested beyond 2 years, non-drug controls in addition to the polydrug controls, a larger battery of neurohormonal measures (e.g. cortisol, oxytocin, prolactin; Parrott, in press), and indices of serotonergic integrity.

Potential causes for the psychobiological variation

This final section will debate possible causes for the variance in findings, and suggest some future research topics. The most crucial factor is probably the amount of drug taken, indeed the contributory the role of lifetime usage has often been noted (Gouzoulis-Mayfrank et al, 2003; Parrott, 2006; Kish et al, 2010; White, 2014). Other potentially important drug factors might be the amount taken at any one session, drug purity, and method of administration. These are more difficult to measure since they are inherently more variable, and may change with greater experience. Indeed they may be closely related to lifetime usage, with chronic tolerance leading to more intensive usage (Parrott, 2005). Tablets have been the traditional vehicle for self-administration, but in recent years they have been complemented by 'bombs' (MDMA powders wrapped in Rizla papers and swallowed), and nasal insufflation (snorting as in cocaine). The functional implications of these newer, and potentially stronger methods of self-administration, need to be empirically investigated.Very heavy users may also inject, but again the practical implications have rarely been studied. Samuel et al (2013; full report Downey et al, in press). found significant deficits in gross psychomotor skill in drug-free MDMA polydrug injectors, but this finding needs to be empirically replicated.

Environmental factors when on drug are also important, especially the physical and psychosocial conditions during consumption. Ambient and core body temperature, crowding, prolonged dancing and loud music can combine to produce hyper-stimulation, potentially through the integrative actions of the HPA axis. The master neurohormone for the HPA axis is cortisol, and this is increased significantly by MDMA in the laboratory, while the degree of cortisol increase can be dramatically higher, around 800%, when MDMA is

taken at clubs (Parrott et al, 2008). Three-month hair samples revealed that regular Ecstasy/MDMA users have cumulative cortisol levels 400% higher than non-user controls (Parrott et al, 2014). Cortisol provides a simple biological index for the level of energetic stress experienced by the organism; hence it may provide a useful measure for future research. In particular, it could be employed to test the bio-energetic stress model for humans (Parrott, 2006). This model is closely based on laboratory animal data which shows a wide range of environmental and drug interactions (Huether et al, 1997). The model proposes that the extent of bioenergetic stress experienced by the organism, will determine the degree of psychobiological problems it develops.

Another important neurohormone is oxytocin, since it is involved in affiliative behaviours, and may be central for the pro-social effects of recreational Ecstasy/MDMA (McGregor et al, 2008; Broadbear et al, 2014). However, again the empirical findings are surprisingly variable. While one empirical study found a positive correlation between the extent of oxytocin release and pro-social outcomes in terms of moods (Dumont et al, 2009), several other studies failed to demonstrate the predicted association (Parrott, 2016). Future research might benefit from investigating a wider range of psychobiological dependent variables. Perhapsifferences in oxytocin reactivity could help explain some of the variation in mood reactions to MDMA. Similarly oxytocin may account for the increased libido, and riskier sexual behaviours, of some recreational MDMA users (Theall et al, 2006; May and Parrott, 2015). It may also be important during pregnancy, given its core functions around birth (viz: for birth contractions and subsequent lactation). Hence it would be interesting to replicate the prospective DAISY study (Singer et al, 2012a,b, 2016), using a full battery of neurohormonal measures administered at various time points during pregnancy, and after the birth. Another important group of factors are individual differences, since they may contribute to the variation in research outcomes. Individual differences in personality and psychiatric wellbeing have been investigated with many types of psychoactive drug, including alcohol, nicotine, cannabis, and the opiates. Yet surprisingly they have not featured strongly in MDMA research, despite potentially helping to explain why some individuals may be more far susceptible to the development of neuropsychobiological problems than others. Genetic factors have also been investigated in a few studies, but again they need to be monitored more widely.

In summary, MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy remains a popular illicit drug, despite the many long-term negative consequences associated with repeated use. Moreover recreational use is a continued public health concern, particularly given recent increases in MDMA-related deaths (Anderson, 2014), and increasing tablet strength (Global Drugs Survey; Winstock, 2015), which reported tablets containing up to 200mg MDMA. With these higher strength supplies, the repeated use of MDMA may adversely affect the 5HT system after fewer lifetime exposures, than shown in earlier studies (Kish et al, 2010; Erritzoe et al, 2011; others). In a recent review of the psychobiological problems associated with these serotonergic changes, it was clear that a wide range of psychobiological functions could be impaired (Parrott, 2013b). Yet these deficits could often be quite subtle, agreeing with the conclusion offered by Jacobs and Furnell (1997) that: 'Serotonin is an enigma, it is involved in everything, but responsible for nothing'. The psychological deficits apparent in many recreational users fit this model. Hence we urge future research to be theoretically driven, and empirically test potential explanations - such as the energetic stress model. Certainly any explanatory model will need to consider a range of drug and non-drug factors as potential causative agents. The research might also help elucidate the diverse psychobiological functions subserved by serotonergic neurotransmission, and their potential modulation by neurohormonal influences.

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