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Neurological and cognitive alterations induced by MDMA in humans

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Abstract

3,4-Methylenedioxymethamphetamine, generally referred to as MDMA or 'ecstasy', is a ring-substituted phenethylamine stimulant which produces powerful empathogenic effects. Use of MDMA remains popular despite prohibition, and potential long-term negative consequences of repeated use. MDMA produces its acute subjective effects primarily by stimulating the release of serotonin via action at the serotonin transporter (SERT). There is evidence that MDMA administration may lead to long-lasting neurotoxic effects on serotonin neurons in primates, and reductions in markers of central serotonin axons, and axon terminals in animals. In humans, demonstration of serotonergic neurotoxicity is much more difficult to identify, and much of the research is complicated by confounding issues of polysubstance use, genetic and environmental factors and reliance on self-reports of previous drug use. We do not review the mechanisms for neurotoxicity in detail as they are covered elsewhere in this special issue. There is a large body of literature, however, which has investigated potential cognitive and neurocognitive consequences of repeated MDMA use. Here we review the literature on cognition, and neuroimaging studies that have investigated structural and functional brain changes associated with ecstasy use.

Key Words: MDMA; ecstasy; cognition; neurotoxicity; memory; fMRI; PET; substance use; humans.

Introduction

MDMA, originally patented by Merck in 1914 and resynthesised by Shulgin in 1965 (Shulgin & Shulgin 1991) was developed for use as an aid to psychological therapy (Beck & Rosenbaum, 1994). In line with its empathogenic effects (Dumont & Verkes, 2006) MDMA was found to be useful for increasing openness in marriage and relationship therapy (Greer & Tolbert, 1998). MDMA, and its illicit forms ecstasy/Molly/Magic, became a popular club drug from the 1980s onwards (Parrott, 2001; Schuster *et al.*, 1998). Despite MDMA's prohibition, according to the World Drug Report (WDR) (United Nations Office on Drugs and Crime, UNODC 2019), it was estimated that there were 21.3 million MDMA users globally in 2019, representing 0.4% of adults aged 16-54. After Oceania (2.2%), Europe and North America have the highest estimated use (both at 0.9%). However, household population estimate surveys in various countries indicate that use is highest in the 16-25 age group (e.g. Broadfield, 2017), with a recent survey in 15-16 year olds reporting lifetime prevalence at 2% (EMCDDA, 2016). MDMA/ecstasy is usually administered orally with peak plasma concentrations around 1.5-3.0 hours after administration (see de la Torre *et al.* 2000 for a full discussion of pharmacokinetics of MDMA in humans). In the brain, MDMA agonises monoamine neurotransmitters, causing the release of serotonin, dopamine and norepinephrine, in addition to blocking their reuptake (Berger *et al.*, 1992; Nichols *et al.*, 1982). As such, there are increased levels of serotonin in the synapse, which cause the majority of the MDMA-specific primary subjective effects (Green *et al.*, 2003). However, damage to the serotonin system could occur after repeated use causing a range of neurological and cognitive alterations. Indeed, studies on the effects of recreational use of ecstasy have reported elevated depression (MacInnes *et al.*, 2001), heightened impulsivity (Morgan *et al.*, 2006) and cognitive deficits (Roberts *et al.*, 2016a) after use. Below we summarise studies investigating neurological alterations in recreational users and the potential cognitive consequences of such alterations.

Neurological alterations in human recreational users

In humans, several neuroimaging techniques have been used to assess structural and functional brain changes associated with chronic use. These include functional and structural Magnetic Resonance Imaging (MRI), functional Near-Infrared Spectroscopy (fNIRS), Electroencephalography (EEG), Single Photon Emission Computerized Tomography (SPECT), and Positron Emission Tomography (PET).

Magnetic Resonance Imaging

Using a structural MRI analysis technique called voxel-based morphometry, Cowan *et al.* (2003) reported that ecstasy users had reductions in grey matter volume relative to non-users, in areas of the frontal cortex (Brodmann's Area - BA 45), and temporal cortex (BA 21) involved in semantic memory retrieval. Reductions were also observed in BA 18 in the occipital lobe, an area of the visual cortex, which the authors note is important for visual learning. Decreased grey matter volume was also reported in the cerebellum, and the pons. Cowan *et al.* (2006) followed this structural imaging study with a functional MRI study to investigate brain activation in the visual cortex during photic stimulation. However, no between group differences were observed between MDMA users and non-users. Lifetime episodes of MDMA use was correlated with activated pixels for photic stimulation, but not BOLD signal change. Thus, the functional imaging study showed little evidence to support differences observed in the structural imaging study.

Daumann and colleagues conducted a series of fMRI studies to investigate brain activity during cognitive performance in MDMA users. In Daumann *et al.* (2003a) differences in activation between heavy MDMA users, moderate MDMA users and non-user controls were investigated using a memory updating task (the *n*-back). No performance differences were observed between the three groups. Moreover, there were no significant differences in brain activity using a conservative level of significance ($p < .05$ corrected), though when using a less conservative threshold of uncorrected $p < .01$, differences did emerge in the right parietal cortex whereby both users groups showed greater activation than controls. Conversely, heavy users had weaker activation in frontal and temporal areas than moderate users. The authors suggest that this study indicates subtle changes to brain function that associated with MDMA use. In a further study to attempt to control for the effects of concomitant use of other drugs, Daumann *et al.* (2003b) compared pure ecstasy users, polyvalent ecstasy users (concomitant use of ecstasy and amphetamines and cannabis) and nonuser controls on the *n*-back task. The pure ecstasy user group showed reduced activity in the temporal and angular gyri compared to both control groups, although no task performance differences were observed. Furthermore, Daumann *et al.* (2005) report reduced hippocampal activity in ecstasy/polydrug users relative to cannabis only users, during retrieval of episodic memory. However, no behavioural differences are reported. Taken together these findings suggest that there are structural changes which may be present in the absence of observable behavioural changes.

In Moeller *et al.* (2004), ecstasy users, relative to non-users, showed greater activity in the left medial and superior frontal gyri; the left thalamus, caudate and putamen; and the right hippocampal formation during immediate and delayed recall performance (though no performance differences were observed). However, the effect was no longer significant in the frontal cortex after controlling for cannabis use. Conversely Jacobsen *et al.* (2004) report lower hippocampal activity in

adolescent MDMA users relative to controls, and poorer performance on a selective and divided attention task. The authors suggest that hippocampal function may recover following prolonged abstinence.

A final fMRI study by Roberts and Garavan (2010) found that ecstasy users showed greater activation in right middle and inferior frontal gyri, right middle frontal gyrus and right inferior parietal lobule, compared to controls, during a response inhibition task. Greater activity was also observed in the user group following task performance errors in the right middle and inferior temporal gyri. Due to there being no task-related performance differences, the increase in activation may be attributed to MDMA users working harder to achieve the same level of performance as non-users. Support for this notion comes from several EEG studies, which report atypical Event-Related Potentials (ERPs) despite similar behavioural performance between users and non-users on a range of executive functioning tasks (Roberts *et al.*, 2013 a, b & c).

There are also several fMRI studies that report no differences between users and non-users. For example Jager *et al.* (2008) show no effects of ecstasy on brain activation or performance on a working memory task, and an attention task. Ecstasy use did however predict lower activity in left dorsolateral prefrontal cortex (DLPFC) during associative learning, along with *higher* activation of the right middle occipital gyrus.

Functional Near-Infrared Spectroscopy

Functional Near-Infrared Spectroscopy (fNIRS) is a newer neuroimaging modality relative to fMRI, which uses near-infrared light to measure changes in oxygenated and deoxygenated haemoglobin from baseline in the cerebral cortex. Due to the penetration depth of infrared light, fNIRS is limited to imaging superficial layers of the cortex, and does not have the spatial resolution of fMRI (and so cannot assess subcortical structures). However, it has been used to assess prefrontal cortex activity in ecstasy user samples, and the data so far have been more consistent than the published fMRI data.

The first of the 4 studies that have been published so far using fNIRS (Roberts *et al.*, 2015), assessed 20 ecstasy/polydrug users, 20 non-ecstasy polydrug users, and 20 drug naïve controls during performance of a multitasking stressor. There were no between group differences in behavioural performance. However, ecstasy users displayed reduced oxygenated haemoglobin (O₂Hb) in the left and right DLPFC. The direction of oxygenation change here is not consistent with that of the following three studies by our group, or with the hypotheses of recruitment of additional resources to attain similar performance as non-users. Instead an explanation of these findings was

offered as potentially a result of protracted/prolonged vasoconstriction (i.e. less pronounced oxygenation due to less blood flow altogether). This was suggested due to one of the sympathomimetic effects of ecstasy being vasoconstriction (narrowing of blood vessels, leading to slowing/blocking of blood flow), which has been observed not only acutely, but for prolonged periods of abstinence (e.g. Chang et al., 2000).

In a further fNIRS study from the same group, inhibitory control was assessed with a random letter generation task (Roberts & Montgomery 2015a). Ecstasy users (n=20) and controls (n=20) performed at a similar level on the task. However differences in blood oxygenation in the inferior right medial prefrontal cortex, and bilateral DLPFC were observed. In each case users had greater O₂Hb than non-users. This provides support for the notion that increased oxygenation in areas of the prefrontal cortex reflect recruitment of additional resources to maintain performance at a similar level to controls. The authors suggest that this reflects a neurobiological change that manifests prior to any performance deficit.

Similar findings were observed in a study investigating word fluency performance in ecstasy users and non-user controls (Roberts & Montgomery, 2015b). Performance on the Chicago Word Fluency Task was similar in both groups. However ecstasy users showed greater O₂Hb in the left DLPFC and the right medial PFC. Changes in O₂Hb were also predicted by frequency of ecstasy use, lifetime dose, and recency of use. Furthermore Montgomery et al. (2017) report increased cortical oxygenation in the PFC despite no between group differences in performance in verbal and spatial updating between ecstasy users and non-users.

The findings from fNIRS suggest neurobiological alterations in ecstasy users. However, whilst interpretation of 3 of the 4 studies is consistent with increased effortful cognition, as a compensatory mechanism, the fourth shows effects in the opposite direction, and offers an explanation of ecstasy-related vasoconstriction. None of the studies using fNIRS assessed potential recovery of function following prolonged abstinence. In addition, they are not presently able to indicate whether the participants that show increased activation would develop cognitive deficits in the future. Thus, the proposed notions of neurobiological impairment must be treated with caution.

Molecular Imaging

Molecular imaging techniques e.g. SPECT and PET, have been used to assess the integrity of the serotonin system in ecstasy users. Molecular imaging involves injecting participants with a radioactive tracer (radioligand) which binds to either pre-synaptic serotonin transporter terminals (SERTs) or postsynaptic serotonin (5-HT_{2A}) receptors. As such, the availability of SERTs or 5-HT_{2A}

receptors can be quantified, and the integrity of the serotonin system can be assessed. Due to the selectivity of SERT of 5HT_{2A} specific radioligands, molecular imaging can circumvent the confounding issue of polydrug use, as the major concomitant drugs (alcohol, cannabis and cocaine) are not known to act on the serotonin system to a great extent, which is problematic when interpreting retrospective studies on the effects of ecstasy use.

Our meta-analysis (Roberts *et al.*, 2016b), of molecular imaging studies comparing serotonin transporter availability in current ecstasy/polydrug users relative to controls demonstrated that SERTs were reduced in current users in 11 out of the 14 brain regions measured. This analysis suggests that across the totality of the data, there are consistent reductions in SERT in every neocortical (frontal cortex, parietal cortex, temporal cortex, occipital cortex, and dorsolateral prefrontal cortex) and limbic region (anterior cingulate, posterior cingulate, hippocampus, amygdala, insula). However, there are studies that suggest that effects on SERT may recover following abstinence. For example, in Buchert *et al.* (2003), SERT reductions in the caudate and thalamus were observed in current users, relative to controls, but not former users. Moreover, positive correlations between abstinence and DVRs of SERT were observed in a follow up study (Buchert *et al.*, 2004), further supporting the notion that SERT damage can be reversed after cessation of use. Thomasius *et al.* (2006), observed that ecstasy related reductions in SERT at baseline in the mesencephalon, were no longer present at follow up, following abstinence or significant reductions in use. To consolidate this, Sudhakar *et al.*, (2009) report no differences in SERT distribution volume ratios in former users compared to polydrug and non-drug user controls. In addition McCann *et al.* (2008) report reduced SERT binding in several brain regions (occipital cortex, parietal cortex, temporal cortex, anterior cingulate cortex, posterior cingulate cortex, DLPFC and hippocampus), and suggest that SERT DVRs are correlated with duration of abstinence (McCann *et al.*, 2005). However, as detailed in Thomasius *et al.* (2006) potential SERT recovery is not necessarily reflected by recovery of cognitive function changes. They observed that whilst SERT availability showed partial recovery in users who reduced use, former ecstasy users in this study showed no sign of improvement in verbal memory (following 2.5 years of abstinence), which may reflect persistent cognitive effects attributable to MDMA neurotoxicity. Thus, a full understanding of the reversibility of MDMA-related serotonergic system alterations has yet to be fully elucidated.

Cognitive alterations

Acute effects of MDMA on cognitive function

As mentioned above, MDMA is a potent agonist of the monoamine neurotransmitters serotonin, dopamine and norepinephrine. Such changes in neurotransmitter levels affect cognitive processes; this section will review studies on acute administration in a laboratory setting.

A comprehensive review of placebo controlled MDMA administration studies found that acute effects of MDMA on cognition had been assessed in 3 domains – executive functioning, attention and visual, visuomotor and auditory function (Dumont & Verkes, 2006). The evidence base was limited with only two tasks (Tower of London; word fluency) in one study (Lamers *et al.* 2003) assessing executive functioning and no studies assessing memory. Of the 11 studies using attention tasks, none reported significant MDMA-related changes after administering doses ranging from 75-125mg. Six studies assessed motor function and of these, one study reported improvement in two tasks of motor function after administration of 75mg MDMA (Lamers *et al.* 2003). More recently, Kuypers & Ramaekers (2005; 2007) found that 75mg MDMA impaired performance in immediate and delayed recall, spatial memory, but not syntactic reasoning or the Digit Symbol Substitution Test (DSST). Interestingly, the deficits were no longer present during a 24-hour withdrawal period when 5HT levels would be lower than during intoxication, contrasting with the proposed mechanism for MDMA-related cognitive impairments after long-term use (Morgan *et al.* 1999). To further elucidate the mechanism of acute MDMA-related memory impairment, van Wel *et al.* (2011) administered 75mg MDMA with either a 5HT_{1A} (pindolol) or 5HT_{2A} (ketanserin) receptor blocker. MDMA-induced impairments in verbal memory, but not spatial or prospective memory, were prevented by co-administration of ketanserin, suggesting a role for the 5HT_{2A} receptor in acute verbal memory impairments. de Souza Fernandes Perna *et al.* (2014) found that 75mg of MDMA impaired visual, verbal and spatial memory, though accuracy on the Sternberg memory test was improved in the MDMA condition. Using a higher dose than previous studies, Dumont *et al.* (2008) found that 100mg MDMA impaired performance in delayed recall and psychomotor attention, showing a dose response effect. In addition, using an automated battery of cognitive tasks – the CANTAB - Hasler *et al.* (2009) found that 1.6mg/kg MDMA impaired sustained attention and visuospatial memory performance.

However, the studies reviewed thus far on acute effects on cognitive function were all performed during the day time in a laboratory setting. This does not mirror the conditions under which individuals would usually use ecstasy (night time, re-dosing). To illustrate the confounding factors of naturalistic MDMA administration, Kuypers *et al.* (2008) compared the effects of placebo vs. 125mg of MDMA (administered as 2 separate doses of 75 & 50mg over the course of an evening). Both MDMA and sleep deprivation impaired cognitive performance progressively over time, highlighting the importance of ecological validity in lab studies. Following a similar protocol, the

same lab assessed the effects of MDMA vs placebo at 4 time points over a single night. MDMA selectively impaired tracking performance and divided attention, but not impulsivity (Kuypers *et al.* 2007). More everyday aspects of memory have also been impaired acutely by MDMA. For example, Ramaekers *et al.* (2009) found that 75mg MDMA impaired prospective memory performance by increasing the number of failures in No-go trials, and that failures were positively correlated with plasma levels of MDMA. Furthermore, using fMRI, the same study found that MDMA reduced deactivation in bilateral inferior parietal lobules, which could be responsible for any observed impairments in prospective memory. Finally, Doss *et al.* (2018) found that administration of 1mg/kg MDMA reduced the encoding of both positive and negative emotional information, which was reflected during the retrieval phase. This is particularly salient as it provides insight in to the mechanism via which MDMA might be useful for the treatment of PTSD (Yazar-Klosinski & Mithoefer, 2017).

Long term cognitive deficits in recreational users

The long-term effects of MDMA administration in laboratory animals have been assessed in various domains. The consensus from a recent systematic review of studies investigating the effects of MDMA administration on cognitive function in animals concluded that there was no long-term effect of doses less than 3mg/kg on cognitive function, and little evidence for impairment in the majority of studies using doses larger than 3mg/kg. The authors note that while the preclinical evidence for cognitive deficits is weak, there are confounding factors in human recreational users such as drug purity, environmental conditions and concomitant use of other substances which could result in a different profile of impairment to that seen in animals (for systematic review of the effects of MDMA on animal cognition, see Pantoni & Anagnostaras, 2019). Research on cognitive deficits in ecstasy-polydrug users is derives from early preclinical psychopharmacological work showing dense innervation of serotonin receptors in the prefrontal cortex necessary for performing many higher-order cognitive tasks. While data on long-term abstinence from ecstasy use are limited (>5 years abstinence), many studies have investigated short-medium term cognitive effects in currently abstinent users (> 1 week). This section gives a brief overview of the most robust effects observed in recreational MDMA polydrug users, in declarative memory and higher order “executive” functions which are a set of general-purpose control processes (Miyake & Friedman, 2012) underpinning cognitive function in general.

One of the most consistent findings in studies of human recreational MDMA users is that the exhibit impairments in declarative memory. Similar to the acute effects mentioned above, many studies assessing declarative memory have used immediate and delayed recall of words (Bolla *et al.*

1998; Downey *et al.*, 2015; Parrott *et al.* 1998; Parrott & Lasky 1998; Reneman *et al.*, 2001; Thomasius *et al.*, 2003) and of prose (Bhattachary & Powell, 2001; Krystal *et al.*, 1992; Morgan, 1999; Morgan *et al.*, 2002). While the underlying cause of such deficits is purported to be depleted 5HT, it is surprising that Kuypers and Ramaekers (2005, 2007) found recall deficits acutely after MDMA administration, but not during withdrawal. Moreover, Wunderli *et al.* (2017) investigated declarative memory in pure chronic MDMA users vs. polydrug users and found that the MDMA group, but not the polydrug group, exhibited impairments. It is also clear that level of MDMA use plays a role in the deficits with increases in monthly use (Bolla *et al.*, 1998), amount used in the last year (Price *et al.*, 2014) and total lifetime dose of ecstasy (Gouzoulis-Mayfrank *et al.*, 2000; Downey *et al.*, 2015) all associated with increased impairments. However, Schilt *et al.*, (2007) found that significant impairments in immediate and delayed recall were evident in novice users with low ecstasy exposure suggesting that this cognitive function is particularly susceptible to the effects of MDMA use. There is evidence to suggest that deficits do not improve with prolonged abstinence (Thomasius *et al.*, 2003) suggesting that they may be long-lasting.

Prospective memory (PM) requires an individual to remember to carry out a future intended action e.g. remembering to take medication, and utilises prefrontal executive areas (Okuda *et al.*, 2007). Ecstasy users have exhibited deficits in various aspects of prospective memory. This has been shown by Heffernan *et al.* (2001a; 2001b), who report ecstasy-related impairment on short-term habitual memory subscales of the Prospective Memory Questionnaire (PMQ). Using a more ecologically-valid measure of PM, the “virtual week” task, Rendell *et al.* (2007) observed ecstasy users to be significantly impaired relative to non-users, which remained significant after controlling for cannabis use. Furthermore Rendell *et al.* (2007) suggest that greater PM deficits are apparent in more frequent ecstasy users. Using the Jansari Executive Framework, a virtual reality assessment of executive function and PM, Montgomery *et al.*, (2010) did not find an ecstasy-related deficit any of the PM subscales, and paradoxically higher cocaine use within the sample was correlated with better time-based PM. The use of other substances in ecstasy polydrug users has also emerged as an important factor with Montgomery & Fisk (2007) reporting that deficits in PM in ecstasy users were more highly correlated with the use of cannabis within the sample. To elucidate the relative effects of ecstasy and cannabis on PM, Hadjiefthvoulou *et al.* (2011) used the CAMPROMPT and found the ecstasy using group were impaired in event and time-based PM tasks relative to cannabis users, though level of cocaine use within the ecstasy group was also correlated with deficits. Research has also shown impairments in both subjective and objective measures of PM in ecstasy users suggesting that individuals are aware of their own PM failures (Hadjiefthvoulou *et al.*, 2010). In this study there was also evidence that the impairments improved with increasing abstinence period from MDMA.

Gallagher *et al.* (2014) found ecstasy-related PM impairments which were related to high average session dose (i.e. amount consumed over one night), rather than cumulative lifetime dose. It is clear from the preceding evidence that users of MDMA do exhibit cognitive deficits in PM, but that the concomitant use of other drugs, in particular the use of cannabis, needs to be controlled for.

There have been extensive reports of executive dysfunction in ecstasy users. One possibility is that complex cognitive processes such as executive function rely heavily on the prefrontal cortex (PFC). The PFC is richly innervated with 5HT_{2A} receptors, and downregulation or degradation of these structures, as discussed in the imaging studies above, could contribute to such deficits. Indeed there is evidence for the role of 5HT_{2A} receptors in other types of acute MDMA-induced memory impairment (van Wel *et al.*, 2011). On some executive function tasks, there are MDMA-related deficits, while on others, the performance is equivocal. Inhibitory control, the ability to inhibit an automatic/dominant response when it is not appropriate does not appear to be affected by ecstasy use using a range of paradigms. Studies using the Stroop task (Back-Madruga *et al.*, 2003; Croft *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2000; Halpern *et al.*, 2011; Morgan *et al.*, 2002; Wagner *et al.*, 2012), Random Letter Generation (Fisk *et al.*, 2004; Fisk & Montgomery 2009; Montgomery *et al.*, 2005; Murphy *et al.*, 2011), and Go/NoGo paradigms (Gouzoulis-Mayfrank *et al.*, 2003; Hanson & Luciana, 2010; Roberts & Garavan, 2010) do not report ecstasy-group differences relative to controls. When investigating task switching, the ability to switch attention back and forth between different tasks/aspects of the same task, there is limited evidence for performance decrements related to ecstasy use. Some studies show that ecstasy users have lower overall scores, but that differences fail to reach statistical significance (e.g. Wunderli *et al.*, 2017). Despite the lack of consistent group differences (e.g. Back-Madruga *et al.*, 2003; Dafters 2004; Fox *et al.*, 2001; Hoshi *et al.*, 2007; McCardle *et al.*, 2004; Montgomery *et al.*, 2005; Reneman *et al.*, 2006; Zakzanis & Young, 2001) a recent meta-analysis from our own group, Roberts *et al.*, (2016a) observed that ecstasy users were significantly impaired compared to nonusers in set switching when the data was pooled.

Ecstasy also appeared to consistently impair spatial working memory in earlier studies, with dose (Hanson & Luciana, 2010) and frequency of use (Montgomery & Fisk, 2008) emerging as important predictors of impairment. The effects of ecstasy on spatial WM (in a spatial updating task) do not appear to be reversed with prolonged abstinence (> 6months), and remain significant after controlling for cannabis use (Montgomery & Fisk, 2008). An initial meta-analysis of visuospatial memory deficits in 2012 found that ecstasy-related deficits in various aspects of performance, though these decrements were not related to indices of past ecstasy use (Murphy *et al.*, 2012). An updated systematic review from the same group (Murphy *et al.*, 2021) concluded that the evidence for visuospatial working memory deficits in ecstasy users is contradictory and there is need for

better controlled studies in this function. Deficits in spatial memory would be consistent with the findings of Cowan *et al.* (2003) who reported decreased activation in BA 18 in ecstasy users.

One of the seminal executive functions that is synonymous with the concept of working memory as a whole is memory updating – the ability to store, review and manipulate task relevant information. A range of paradigms have been used to assess this function in ecstasy users, with consistent impairments observed in letter updating (Montgomery & Fisk, 2008; Montgomery *et al.*, 2005), with higher levels of use leading to poorer performance. Similarly users perform worse on computation span than controls, which does not improve with abstinence (Wareing *et al.*, 2004; Wareing *et al.*, 2005). However, studies using less demanding updating tasks such as backwards digit span have reported no between group differences when compared to nonusers (Bedi & Redman, 2008; Bhattachary & Powell, 2001; Croft *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2003; Nulsen *et al.*, 2011; Reay *et al.*, 2006; Thomasius *et al.*, 2006). To support the effects of cognitive demand, easier n-back tasks rarely yield ecstasy related cognitive deficits (Daumann *et al.*, 2003b; Daumann *et al.*, 2004; Gouzoulis-Mayfrank *et al.*, 2003). It is worthy of note that one study utilising complex spatial and verbal memory updating tasks failed to find ecstasy-related performance deficits, but ecstasy users did exhibit significant changes in oxygenated and deoxygenated haemoglobin from baseline in areas of the PFC compared to nonusers (Montgomery *et al.*, 2017). The authors propose that this indicates increased cognitive load, and that increases in oxygen turnover during the task in ecstasy users suggest that they are working harder to prevent a performance decrement

Access to semantic memory (retrieval of words, and ability to access long term memory), which relies heavily on the DLPFC (Stuss *et al.*, 1998) has been assessed in ecstasy users with the Chicago Word Fluency Task (CWFT) and Controlled Oral Word Association Task (COWAT). Ecstasy-related deficits are apparent in written word fluency using the CWFT (Fisk & Montgomery, 2009; Montgomery *et al.*, 2005; Montgomery *et al.*, 2007), yet this seems to be less problematic in its oral format (FAS task, or COWAT), perhaps due to the oral version being much shorter and not placing sustained load on the DLPFC (e.g. Semple *et al.*, 1999). Using these fluency measures Montgomery *et al.* (2005; 2007) found that ecstasy users were impaired relative to nonusers, and performance decrements increased as task difficulty increased, with levels of both ecstasy and cocaine use emerging as important factors. In a further study from the same group, deficits remained significant after controlling for differences in self-reported sleep quality (Fisk & Montgomery, 2009). Heffernan *et al.* (2001) observed similar deficits after controlling for the use of other drugs. However using a simpler oral variant of the task (the COWA), many studies have failed to find ecstasy-related deficits (Bedi & Redman, 2008; Croft *et al.*, 2001; Halpern *et al.* 2004; Hanson & Luciana, 2010; Morgan *et al.*, 2002). While there is limited evidence of impairments using this variant, Bhattachary and Powell

(2001) observed ecstasy-related deficits using the COWA with all three MDMA user groups (novice, regular currently abstinent) performed significantly worse than non-users. Hanson and Luciana (2004) found that ecstasy users had equivocal performance, but committed more rule breaking errors, and those who met the DSM criteria for MDMA abuse produced significantly fewer words than nonusers, indicating that heavier, more problematic use may predispose to cognitive deficits. More recently Raj *et al.* (2010) found deficits on a novel semantic fluency task to be related to cannabis use and not ecstasy use. In summary, access appears to be affected where task difficulty is high, and where there are confounding factors such as heavier use.

Confounding factors in studies of human ecstasy users

The prohibition of MDMA raises a number of methodological caveats for researchers studying the drug. Due to its illicit nature, it is more difficult to perform controlled trials on the effects of the drug; for example in the UK, MDMA is a schedule I drug, indicating that it is deemed to have no medical uses or benefits. Consequently there are a limited number of studies investigating long-term neurological and cognitive alterations after administration of MDMA. There are however many recreational users of ecstasy globally (UNODC, 2019). One problem for researchers in this area is that recreational doses of *ecstasy* contain varying amounts of *MDMA*, so it is difficult to make direct comparisons between laboratory studies administering MDMA and field studies of ecstasy users. There was a period of very low purity reported after the peak in use in the late 90s/early 00s, driven by lack of MDMA precursors (Mounteney *et al.*, 2018). Consequently ecstasy contained adulterants and other substances intended to mimic the effects of the drugs such as Paramethoxymethamphetamine (PMMA), which could lead to other harms and differing neurological and cognitive alterations (EMDCCA, 2003; Nichol *et al.*, 2015). Recent statistics on seizures of ecstasy between 2010 and 2016 suggest that purity is now comparatively higher with fewer adulterants (UNODC, 2019), so current users of ecstasy will be using fewer adulterants than those using 10 years ago. Similar to the presence of adulterants and substitute drugs, polydrug use can exacerbate the cognitive impairments caused by ecstasy use, due to interactions between drugs and their metabolites. Polydrug use is very common among recreational ecstasy users, with relatively few studies utilising samples of ecstasy only users (e.g. Halpern *et al.*, 2004; Wunderli *et al.*, 2017). As such, the observed neurological and cognitive alterations in human users are likely to be a product of polydrug use. Moreover some ecstasy polydrug combinations are believed to be more neurotoxic than others, with cocaine increasing the neurotoxic potential and cannabis decreasing it (Sarne & Keren, 2004). See Carvahlo *et al.* (2012) for review of polydrug use and effects of MDMA.

There are a number of factors, both physiological and environmental, which could exacerbate the toxic effects of MDMA, through their interaction with individual differences in pharmacokinetics (Capela *et al.*, 2009). For example, females are more likely to experience adverse effects, possibly due to the effects of hormones on pharmacokinetics (Liechti *et al.*, 2001; Simmler *et al.*, 2011) and various genetic polymorphisms can affect metabolism of both MDMA and serotonin (Hysek *et al.*, 2012; Martin-Santos *et al.*, 2010; Rietjens *et al.*, 2012; Tucker *et al.*, 1994), affecting overall neurological and cognitive alterations. In addition the environmental conditions when using ecstasy can exacerbate any adverse effect with higher ambient temperature (Capela *et al.*, 2006; Green *et al.*, 2003) and increased physical activity (Parrott *et al.*, 2006) emerging as significant factors.

Taking these confounding factors into account, future research may benefit from more longitudinal research with prospective users which can track cognitive and neurological changes associated with MDMA use over time. Longitudinal research, in combination with toxicological testing to substantiate recent use (and presence of adulterants and polydrug use), as well as genotyping techniques may allow us to detect magnitude of MDMA related effects at the individual level and detect genotypic vulnerabilities to cognitive/neurological changes associated with ecstasy/MDMA use.

Conclusions

There are many reports of ecstasy related changes to cognition, brain structure, and brain function. The narrative from functional neuroimaging studies is that haemodynamic changes are evidence of serotonin system alterations. One problem with this assumption is that most of the samples in these studies are small, with heterogeneity across studies in their definitions of user, and non-user samples. There is heterogeneity in the interpretation of results whereby increased or decreased activity is described as reflecting serotonergic changes – regardless of performance on tasks. Such studies often are not designed in a way that is able to assess reversibility of effects following abstinence. Moreover, there is often a high occurrence of concomitant drug use in the ecstasy samples, meaning that whilst this is often statistically controlled for – results should still be treated with caution. The confounding effect of polydrug use is less problematic for the molecular imaging studies, where serotonin specific radioligands are used to assess SERT density. As such the molecular imaging research is robust in demonstrating neuroadaptation associated with repeated MDMA use. However the clinical significance of this remains speculative. The purity and quantity of MDMA doses cannot be assessed in all studies in this area, which is problematic for assessing how dose

affects magnitude of neurocognitive changes. Such information is crucial to understand given MDMA is now in late stages of clinical trials for use as an adjunct to talking therapy for several mental health conditions.

The consensus of the data in neurological and cognitive domains suggests that repeated use of ecstasy produces short to medium term neurocognitive/neurophysiological changes that are subtle, and are *potentially* reversible over time. However more research is needed to draw firmer conclusions, to assess the potential of polysubstance use to exacerbate functional changes, and to understand how lifestyle or genetic factors interact with MDMA use to produce neurocognitive sequelae.

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