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Review

The spurious relationship between ecstasy use and neurocognitive deficits: A Bradford Hill review

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ABSTRACT

Numerous studies have suggested that MDMA can cause neurocognitive deficits. However, the available data can only suggest an association – rather than a causal relationship – between MDMA use and neurocognitive deficits. The reliability and robustness of this association was evaluated using Bradford Hill's criteria for determining causation in epidemiology research. Several limitations in the literature were found. Studies have recruited people who abuse ecstasy – an illicit drug that does not always contain MDMA. There is inherent risk in consuming impure or falsely identified substances; and using this as a source as for scientific opinion may introduce biases in our understanding the actuals risks associated with MDMA. Importantly, given that ecstasy research is predominately retrospective, baseline functioning cannot be established; which may be influenced by a variety of preexisting factors. Many studies introduce statistical errors by inconsistently dichotomizing and comparing light and heavy ecstasy users, making dose-response relationships inconclusive. When interpreting the ecstasy literature effect sizes are a more meaningful indicator of neurocognitive functioning rather than relying on *p*-values alone. Most meta-analyses have failed to find clinically relevant differences between ecstasy users and controls. There is also consistent evidence of publication bias in this field of research, which indicates that the literature is both biased and incomplete. Finally, suggestions for improving the ecstasy literature are provided.

Introduction

Over the past 30 years, thousands of papers have been published documenting the neurotoxic and harmful effects of 3,4-methylenedioxymethamphetamine (MDMA) (Rogers et al., 2009). The idea that MDMA may have neurotoxic effects first originated from preclinical studies which found neurotoxicity in rats (Baumann, Wang, & Rothman, 2007) and non-human primates (Green, Cross, & Goodwin, 1995). However, Green, King, Shortall, and Fone (2012) claim that due to a slower pharmacokinetic profile in humans than rodents and monkeys preclinical models of MDMA neurotoxicity may not accurately reflect human processes. Parrott (2012) responded to this paper claiming that there is "no need for translation" because the human literature already shows a conclusive relationship between MDMA and neurotoxicity (Parrott, 2012). However, this claim is based on a body of literature with many methodological issues (Gouzoulis-Mayfrank & Daumann, 2006a, 2006b). While some researchers suggest that MDMA is certainly damaging (Parrott et al., 2014), others have questioned this assumption (Doblin et al., 2014).

MDMA was placed under schedule I status before researchers were able to investigate the potential medicinal properties and the actual risks associated with MDMA. This required researchers to study the effects of MDMA indirectly by looking at the effects of ecstasy, where purity and dosing is variable (see: Gouwe, Brunt, Laar, & Pol, 2017; Saleemi, Pennybaker, Wooldridge, & Johnson, 2017; Tanner-Smith, 2006; Vogels et al., 2009). A sampling bias is created by only allowing researchers to examine the small minority of people (about 6.5%) who are willing to illegally consume ecstasy (National Institute of Drug Abuse, 2013). Further, some studies have recruited friends and acquaintances to participate in research (Parrott, Lees, Garnham, Jones, & Wesnes, 1998; Parrott, Lock, Conner, Kissling, & Thome, 2008), which may introduce potential sampling bias.

This review assesses the literature using the Bradford Hill criteria for epidemiological research (Hill, 1965) – a technique often used to evaluate the quality evidence between a presumed cause and an observed effect (Boniface, Scannell, & Marlow, 2017; Dickerson, Johnston, Delea, White, & Andrews, 1996; Holt & Peveler, 2006; McDonald & Strang, 2017; Perrio, Voss, & Shakir, 2007). Hill proposed that when assessing an association between a particular exposure and its consequences, nine factors should be considered. These factors are: the strength of the association, consistency, temporality, theoretical plausibility, and specificity of the association; the biological gradient (dose-response relationship); coherence; experimental evidence; and analogy. Each criterion is discussed in more detail below.

The need for this review stems from the fact that MDMA is still a schedule I drug, making it difficult to investigate the actual risks and potential clinical benefits (Nutt, King, & Nichols, 2013). Given MDMA's scheduling status, research on the drug has primarily included people

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who abuse a variety of drugs which include ecstasy. The neurocognitive deficits associated with MDMA may actually be attributed to drug abuse in general rather than deficits caused by MDMA specifically (Gouzoulis-Mayfrank & Daumann, 2006a, 2006b). MDMA has been shown to be a useful adjunct to psychotherapy for people with PTSD (Amoroso & Workman, 2016; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011; Oehen, Traber, Widmer, & Schnyder, 2012). Although the FDA has recently allowed for phase 3 clinical trials of MDMA-assisted psychotherapy, reports are still being published on the neurocognitive deficits associated with ecstasy use. These studies typically contain many limitations that will be elucidated throughout this review.

Strength of association

Hill suggested that a strong association is more supportive of a causal relationship than a weaker association (Hill, 1965). The strength of an association – or substantive significance – is most often reported as effects sizes which Cohen (1992) categorized as small ($d \leq 0.2$), medium ($d = 0.5$), or large ($d \geq 0.8$). If ecstasy use were strongly associated with neurocognitive deficits, meta-analyses comparing ecstasy users to controls would show medium to large effect sizes.

Rogers et al. (2009) conducted a comprehensive review including five systematic syntheses, 110 controlled observational studies, and 307 uncontrolled studies published before 2007. Overall, only small effect sizes were reported for all of the outcomes assessed (e.g. attention, executive function, memory, learning, and psychomotor speed). Since Rogers et al. published their review three relevant meta-analyses have been published. Nulsen, Fox, and Hammond, (2010) found small effect sizes in verbal short-term memory ($g = -0.40$; 95% CI −0.59, −0.21), verbal working memory ($g = -0.37$; 95% CI (−0.51, −0.23) and visuospatial short-term memory ($g = -0.25$; 95% CI −0.49, −0.02) and a medium effect size in visuospatial working memory ($g = -0.60$; 95% CI −0.85, −0.36). However, this was followed by a meta-analysis of 40 studies, specifically focusing on ecstasy use and visuospatial memory, which found only small effect sizes (Murphy et al., 2012). Murphy et al. (2012) reported effects sizes for three of the four categories assessed including "recall or recognition of the spatial distribution of individual stimulus elements" ($g = 0.394$; 95% CI −0.608, −0.180), "recognition of figures" ($g = -0.379$; 95% CI −0.585, −0.173), and "reproduction/production of figures" ($g = -0.247$; 95% CI −0.384, −0.109). Murphy et al. (2012) were unable to report an effect size for "judgements of visual/spatial stimulus characteristics" because there was significant heterogeneity in the tasks employed between studies.

The most recent meta-analysis conducted by Roberts, Jones, and Montgomery (2016) included 39 studies, which assessed group differences in four domains of executive function, which resulted in small effect sizes in categories with significant results. These domains included access (SMD = −0.33; 95% CI − 0.46, −0.19), switching (SMD = −0.19; 95% CI − 0.36, −0.02), updating (SMD = −0.26; 95% CI − 0.37, −0.15), and inhibition (no significant differences between groups).

In summary, most meta-analyses on ecstasy users and controls only report small effect sizes in a variety of neurocognitive domains. This would suggest that there is little support for a strong association between ecstasy use and neurocognitive deficits.

Consistency of association

Hill suggested that a causative association should be consistent across studies conducted at different times, locations, and populations (Hill, 1965). Taylor, Greene, Morgan, and Munafò (2011) analyzed how some specific variables have contributed to the inconsistent results found in the ecstasy literature. With respect to time, studies published on ecstasy users have been inconsistent, with progressively smaller effect sizes being published in more recent years (Taylor et al., 2011). This is not a problem only seen in ecstasy literature however. Ioannidis (2005a), points out that initial findings are often exaggerated, which may be attributed to the academic incentive to rapidly publish lower quality studies over more rigorous (albeit expensive and time consuming) studies (Smaldino & McElreath, 2016).

Inconsistencies were also found with respect to the origin of the study. Taylor et al. (2011) found that studies conducted in the United States reported significantly larger effect sizes than those conducted in Europe, which may be related to the hypercompetitive academic climate in the United States compared to Europe (Fanelli & Ioannidis, 2013). Though this is the only study to systematically analyzes the inconsistencies in ecstasy research, many have commented on the equivocal and often contradictory findings in the field (e.g. Gouzoulis-Mayfrank & Daumann, 2006a, 2006b; Grob, 2000; Rogers et al., 2009).

Another issue in this field of research is publication bias. Results that align with a researcher's hypothesis are more likely to be published while null findings often stagnate in the "file-drawer" (Dubben & Beck-Bornholdt, 2005; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). There is consistent evidence of publication bias in the ecstasy literature (Cole, 2014; Roberts et al., 2016a; Rogers et al., 2009; Sumnall & Cole, 2005) meaning that the published studies are not completely representative of the evidence available. To quantify the extent of publication bias in meta-analyses Rosenthal (1979) developed the fail-safe N, which is the number of null findings (where the effect is equal to zero) necessary to make the results of a meta-analysis insignificant ($p > 0.05$). Verbaten (2003) provides a meta-analysis on memory deficits in ecstasy users and found that only 2 unpublished null findings on short term memory would invalidate the results of the meta-analysis. Laws and Kokkalis (2007) conducted a meta-analysis on visual memory and found poorer performance in ecstasy users ($d = -0.27$) but stated that the "fail-safe statistic indicates that no null studies would be required to overturn this effect size". Sumnall and Cole (2005) wrote that only "nine unpublished studies would need to be included to nullify the significant ES [effect size]. Considering the amount of Ecstasy research that does not advance past conference proceedings alone, it is likely that a large body of unpublished work exists". These examples indicate that the available literature is biased and incomplete.

The literature on neurocognitive deficits found in ecstasy users is largely inconsistent. Additionally, there is consistent evidence of selective publishing in ecstasy research.

Specificity of association

According the Hill's criteria, associations are more likely to be causal if specific exposures result in specific outcomes. This would mean that deficits found in ecstasy users should only be attributed to MDMA exposure. Since ecstasy users abuse a variety of other recreational drugs (Gouzoulis-Mayfrank & Daumann, 2006a, 2006b; Rogers et al., 2009) it is difficult to ascertain the actual causes of the deficits. For instance, ecstasy users are more likely than non-users to use cannabis, amphetamine, cocaine, LSD, psilocybin, opioids, ketamine, inhalants, and other drugs that may cause neurocognitive deficits (Fox, Parrott, & Turner, 2001; McCann et al., 2008; Morefield, Keane, Felgate, White, & Irvine, 2011; Roiser & Sahakian, 2004; Schilt et al., 2007; Thomasius et al., 2003; Winstock, Griffiths, & Stewart, 2001). One study of mothers who used ecstasy during pregnancy in addition to significantly more cocaine, LSD, psilocybin mushrooms, and marijuana than non-ecstasy users confidently attributed motor delays in their offspring to the mother's ecstasy use (Singer et al., 2016).

Ecstasy users can also unintentionally consume dangerous substances as ecstasy has been found to have low levels of purity and tablets often contain adulterants (Palamar et al., 2017; Vogels et al., 2009). One study analyzed 1214 tablets sold as ecstasy in the United States and found that only 39% of tablets contained only MDMA, 46% contained no MDMA, and 15% contained mixtures of MDMA and other substances (Tanner-Smith, 2006). Many of the tablets contained

potentially dangerous substances including heroine, dimethoxyamphetamine, phencyclidine, para-methoxy-amphetamine, and cocaine (Tanner-Smith, 2006). A similar but more recent study found that only 60% of samples sold as ecstasy or "Molly" submitted for testing actually contained MDMA (Saleemi et al., 2017). Another study tested hair samples from 90 self-reported ecstasy users and found that 74.4% tested positive for MDMA, 33.3% tested positive for a drug classified as a "new psychoactive substance", and 27.8% tested positive for one or more synthetic cathinones (e.g., butylone, ethylone, pentylone, methylone, alpha-PVP) (Palamar et al., 2017). This suggests that ecstasy users often unknowingly consume drugs with unknown effects. Due to intentional poly-drug use and unintentional consumption of adulterants in ecstasy, it is difficult to attribute deficits specifically to ecstasy.

The outcomes of ecstasy use are equally as ambiguous and have been described as a broad spectrum of symptoms and deficits (McGuire, Cope, & Fahy, 1994). Ecstasy use has been associated with a variety of neurocognitive deficits including domains of memory and intelligence (Parrott, 2013) as well as deficits in psychomotor functioning and visuospatial skills. Ecstasy has been attributed to altered pain perception, disturbed sleep architecture, increased bulimia and chocolate craving, immune system deficits, changes in HPA axis function, and alteration of mood and psychiatric profile (Parrott, 2013). These symptoms represent an array of deficits possibly resembling stochastic noise rather than specific drug effects. An alternative explanation for the broad spectrum of deficits may be that many variables (e.g. premorbid psychiatric disorders, personality and intelligence, genetic factors, polysubstance use, or data dredging) may play a significant role.

There are also differences in results when specific populations are compared. For instance, "ravers" are a convenient sample to study because of their frequent use of ecstasy. However, there are many confounding factors with this population such as frequent circadian rhythm disruptions due to late night dancing, exposure to high ambient temperatures, and frequent dehydration (Cole & Sumnall, 2003). One study that included "atypical" ecstasy users (i.e. those who did not attend raves and had consumed a limited number of other substances) failed to find neurocognitive deficits in the ecstasy using sample (Halpern et al., 2011).

In regards to Hill's criteria, causation would be supported by specific exposures resulting in specific outcomes. However, ecstasy users are often exposed to a variety of substances, both intentionally and unintentionally, resulting in a non-specific array of negative outcomes.

Temporality of association

Hill suggested that an association should have a logical temporal relationship. For example, if MDMA was the cause of neurocognitive deficits in ecstasy users, the deficits should only appear after exposure to the drug and be absent prior to exposure. Since ecstasy studies are primarily observational and retrospective, baseline neurocognitive functioning in participants are largely unknown. Ecstasy users may have unique characteristics, which are not representative of the general population, since only small numbers of people in the general population try the drug. For example, Rogers et al. (2009) points out that intelligence is an important confounding variable in ecstasy research, with ecstasy users often having lower IQs than the control group. Drug-seeking behaviors are associated with unique neurological and psychological characteristics (Koob & Le Moal, 2005), which may be confused as outcomes of ecstasy use rather than the preexisting factors leading to ecstasy use. Some neurocognitive disorders including attention deficit hyperactivity disorder (ADHD) are associated with drug seeking and using behaviors (Biederman, Wilens, Mick, Faraone, & Spencer, 1998; Urcelay & Dalley, 2011). ADHD and traumatic brain injuries, which would have an obvious negative impact on neurocognitive testing, is rarely controlled for in ecstasy research.

One study found that substance-specific genetic factors influenced specific drug use in the future (i.e., cannabis, cocaine, hallucinogen, sedative, stimulant, and opiate use) (Kendler, Jacobson, Prescott, & Neale, 2003). Genetic predispositions for addiction to a variety of drugs have been established (Agrawal & Lynskey, 2008; Kreek, Nielsen, Butelman, & LaForge, 2005). Pardo-Lozano et al. (2012) found that genetic polymorphisms (i.e. *COMT val158met* and *5-HTTLPR* polymorphisms) play a major role in the subjective and physiological effects of MDMA. 5-HTTLPR polymorphisms have been to be linked to depression (Pezawas et al., 2005), which can effect neurocognitive processes (Austin, Mitchell, & Goodwin, 2001). Indeed, one study found that polymorphisms at the 5-HTTLPR effects cognitive function independently of ecstasy use (Roiser, Rogers, Cook, & Sahakian, 2006). Further, the results from Roiser et al. (2006) suggest that neurocognitive deficits found in ecstasy users may be attributed to, and moderated by, genetic variation at the 5-HTTLPR. Since most ecstasy studies are retrospective, baseline cognitive functioning cannot be determined, and as Roiser et al. (2006) have demonstrated many factors including genetic variation, can effect cognitive functioning.

Future research should control for premorbid psychiatric and neurological illnesses such as traumatic brain injury, ADHD, substance use disorder and other mental health problems that can impact neurocognitive functioning. Although prospective study designs could control for this, few have controlled for mental health problems associated with neurocognitive deficits occurring before ecstasy exposure (see: De Win et al., 2006; De Win et al., 2008; Lieb, Schuetz, Pfister, Von Sydow, & Wittchen, 2002; Schilt et al., 2007).

Most prospective studies have small sample sizes and poor methods of recruiting. For instance, one prospective study found significant increases in cortisol and testosterone while dancing on ecstasy which included 12 volunteers – all friends or acquaintances with the key research worker (Parrott et al., 2008). Other studies often use snowballing techniques (Bedi, Van Dam, & Redman, 2010; Dafters, Hoshi, & Talbot, 2004; Jager et al., 2007; Parrott, Sisk, & Turner, 2000) for recruitment, which may cause sampling bias.

One prospective study recruited 149 "almost MDMA-naïve" participants and established baseline neurocognitive functioning in a variety of domains including tests of learning, memory, working memory, and executive functioning (Wagner, Becker, Koester, Gouzoulis-Mayfrank, & Daumann, 2013). One year later 109 of the participants returned for a follow up testing session. The study failed to find significant differences in a variety of neurocognitive outcomes besides delayed and immediate recall of a paired associates learning task (Wagner et al., 2013).

Another prospective neuroimaging study failed to find significant differences in task performance in domains of memory and attention, or brain functioning, after exposure to a single or lose dose of ecstasy (Jager et al., 2007). However, since this study only included 25 participants who had limited exposure to the drug the results are not conclusive.

Theoretical plausibility

In order for a suspected causation to be considered probable, it is helpful if the causation be biologically plausible; however, Sir Arthur Bradford accepted that this criterion cannot be deemed necessary, as "What is biologically plausible depends upon the biological knowledge of the day" (Hill, 1965).

Animal models have provided evidence of MDMA-induced neurotoxicity, with focus placed upon the serotonergic system as the primary target for damage. Oral administration of MDMA has been shown to cause long-term decreases in serotonergic axons of both rats and monkeys (Slikker et al., 1988). Typically, these changes in the serotonergic system are used to gauge the extent of damage caused by the drug. Unlike other amphetamines, MDMA does not appear to damage the dopaminergic system (Steele, McCann, & Ricaurte, 1994), yet it has been suggested that dopamine and its metabolites may still have a primary role in MDMA-induced neurotoxicity. Depleting dopamine and other catecholamines in rats prior to MDMA administration attenuated

subsequent MDMA induced serotonergic damage (Stone, Johnson, Hanson, & Gibb, 1988). This evidence lead to the hypothesis that dopamine, which is released following MDMA administration, travels into nearby serotonergic cells and causes long-term oxidative stress (Green et al., 2012).

The dopamine-mediated hypothesis has been challenged in other studies. For example, Gudelsky (1996) showed that the antioxidants cysteine and ascorbate reduce MDMA neurotoxicity in rats without altering MDMA-stimulated dopamine release, which suggests that toxicity may be a result of oxidative stress caused by its quinone-like metabolites (Green et al., 2012). This hypothesis has been supported by experiments showing that direct injections of MDMA into the brain did *not* yield neurotoxic effects (Mueller et al., 2009), and refuted by experiments showing direct exposure of said metabolites do not replicate MDMA neurotoxicity (Steele et al., 1994).

Use of animal studies has been valuable in unlocking these mechanisms; however, as Green et al. (2012) noted, animal models are not always representative of human physiology. In humans, metabolization of the drug is significantly slower, partially due to the cytochrome p4502D6 enzyme responsible for MDMA metabolism is also inhibited by MDMA itself, allowing more time for humans to utilize neuroprotective factors preventing long-term damage (Green et al., 2012). Furthermore, though many animal studies have examined structural and chemical evidence of neurotoxicity, evidence of behavioral and cognitive deficits has been very limited. Baumann et al. (2007) concluded that outside of one study showing deficits in a delayed non-match to performance task, "the collective behavioral data in rats indicate that MDMA-induced depletions of brain 5-HT have little effect on cognitive processes".

While the current literature still lacks agreement in a concrete mechanism for MDMA neurotoxicity, it does make clear that such toxicity occurs, therefore a mechanism is undoubtedly present. The current hypotheses all lend their own plausibility, and it is important to point out that there might not be one single mechanism, but rather a combination of factors leading to the observed outcomes.

Biological gradient

Hill suggested that a dose response relationship (i.e. more exposures to ecstasy results in more severe deficits) would support a causal association. The preclinical and human literature is quite consistent showing that higher dosages and exposures to MDMA and ecstasy result in increased neurotoxicity and cognitive deficits (Parrott, 2005). However, heavy ecstasy users are also more likely to use larger quantities of other drugs making it difficult to accurately assess dose response relationships (Rogers et al., 2009).

Another important consideration is that many studies arbitrarily define and inconsistently dichotomize their samples of ecstasy users into categories such as light, moderate, and heavy users (Amoroso, 2018). For instance, some studies have categorized light users as those who have had less than 20 lifetime exposures to ecstasy (Butler & Montgomery, 2004; Milani, Parrott, Turner, & Fox, 2004; Parott, Milani, Parmar, & Turner, 2001; Parrott et al., 2000), while others used a cut off less than 50 (Dafters et al., 2004), 100 (Fox et al., 2001), 200 (Verkes et al., 2001), or 400 (Golding, Groome, Rycroft, & Denton, 2007) lifetime exposures (see: Amoroso, 2018). Many studies do not provide methods for establishing their criteria (Butler & Montgomery, 2004; Dafters et al., 2004; Fox et al., 2001; Parott et al., 2001, 2000), while others have used median splits (Halpern et al., 2004; Singer et al., 2016), post hoc assignment (Milani et al., 2004), or "trial and error" (Fisk and Montgomery, 2009). Other studies have established criterion for light, moderate, or heavy ecstasy users by citing other studies – with very different study designs such as case studies (Reneman et al., 2006; Verkes et al., 2001). Reneman et al. (2006) cited Schifano and Magni (1994), which is a case series of 7 individuals on chocolate cravings and other psychopathologies following ecstasy abuse to establish criterion for moderate and heavy ecstasy users. Verkes et al. (2001) set criterion based on recent frequency of use (i.e. consumption in the past two years) rather than lifetime cumulative use. This was justified "because in animal's damage seemed more strongly associated with the former" (Verkes et al. 2001). This is a problematic justification because of the differences between animal and human metabolism of MDMA as well as differences in lifespan. Further, the intensity of ecstasy use in the sample may have been heavier in the years prior to the arbitrarily selected cutoff point.

Most statisticians agree that dichotomizing continuous variables can produce misleading and unreliable results (Altman & Royston, 2006). There is also the potential for the manipulation of criteria to produce significant results. For example, if one set of analyses fails to produce a significant result, criteria can easily and arbitrarily be shifted to ensure significance. The inconsistent dichotomization of ecstasy users into light and heavy users is also problematic when data is aggregated and reported in meta-analyses (Amoroso, 2018).

Coherence

Hill suggested that a "cause and effect interpretation should not seriously conflict with the generally known facts of the biology of the disease." This criterion hard to assess because most of the generally known facts regarding the effects of MDMA exposure are actually based on exposure to ecstasy.

Experiment

The most definitive way to determine causal relationships is by experiment. However, very few clinical trials of MDMA have been conducted. Of those trials most have been focused on the acute effects of the drug or the treatment of posttraumatic stress disorder (PTSD). Only one study has reported on the cognitive effects of a controlled administration of MDMA which found no significant differences in cognitive functioning between those who had received MDMA and controls in a battery of neuropsychological tests (Mithoefer et al., 2011). During a long-term follow-up (between 17 and 74 months after receiving MDMA) 13 out of 19 participants reported improved cognitive functioning while the remaining participants reported no changes (Mithoefer et al., 2013). However, these improvements are likely attributed to reductions in PTSD symptoms. Another study, reporting on the acute effects of MDMA administration, found improvements in psychomotor skills and divided attention tasks (Lamers et al., 2003). This study found no impacts on visual search, planning or retrieval from semantic memory after subjects were administered MDMA (Lamers et al., 2003). However, these results represent the acute stimulant effects of MDMA rather than the long lasting results following its use. Future studies should assess for the long-term neurocognitive effects of consuming MDMA without the confounding variables mentioned above.

Analogy

Hill stated that other potential causes for the disease should be considered before determining that a particular exposure causes a particular outcome. There are many variables that may contribute to the neurocognitive outcomes found in the ecstasy literature. One of the most obvious confounds when comparing cognitive function would be baseline differences in intelligence. Indeed, Rogers et al. (2009) found that in many studies ecstasy users had lower IQ's than the non-ecstasy comparison group.

Ecstasy users also consume other drugs in greater quantities and frequencies than they do ecstasy. Likewise, participants are typically recruited from the "rave" culture, which involves late night dancing in hot environments, disruptions to their circadian rythms, and polysubstance abuse. Premorbid psychiatric disorders such as ADHD, PTSD,

depression, and other disorders commonly associated with drug use and neurocognitive deficits are rarely controlled for in ecstasy studies (Parrott et al., 1998), or only exclude participants who "sought psychiatric help" (MacInnes, Handley, & Harding, 2001). Impulsivity – which can cause obvious reductions in neurocognitive testing – is a common characteristic in people who experiment with psychoactive substances and should be controlled for in studies of ecstasy use (Verkes et al., 2001).

There are a variety of potential explanations for the neurocognitive deficits found in ecstasy users. One potential cause of neurocoginitve deficits found in ecstasy users is acute intoxication during testing. Ecstasy users are more likely to use other drugs including cannabis than non-ecstasy users. While many studies ask participants to refrain from drug use for at least 24 h before testing, few actually perform a urinalysis or breathalyzer to detect drugs of abuse. Similarly, ecstasy studies rarely report the medications their participants are taking, which may include those that impair or enhance cognitive function (i.e. benzodiazepines, opiates, or amphetamines).

Discussion

A substantial amount of money has been spent on research attempting to understand the long-term neurocognitive effects of MDMA – producing thousands of studies with many limitations, biases and controversies (Amoroso, 2016; Grob, Bravo, Walsh, & Liester, 1992). Although there is an extensive body of literature indicating that ecstasy (and therefore MDMA) may be associated with neurocognitive deficits, meta-analyses report asymmetrical funnel plots (Roberts et al., 2016a; Roberts, Jones, & Montgomery, 2016; Rogers et al., 2009; Sumnall and Cole, 2005) and other evidence of publication bias in this field of research. This means that studies failing to find neurocognitive deficits in ecstasy users are likely being completed but not being published.

Another issue with this area of research is the lack of evidence for a biological gradient (i.e. dose response relationship). While several individual studies show evidence of a dose response relationship (i.e. heavier use resulting in more severe deficits) (Fox et al., 2001; Parrott et al., 2000, 2002) most meta-analyses do not (Laws and Kokkalis, 2007; Rogers et al., 2009). This may be attributed to flexibility in data analyses (or data dredging) – found in the ecstasy literature (Amoroso, 2018). Significant differences between light and heavy using groups can be guaranteed if the criteria for defining the groups can be manipulated consciously or unconsciously (Amoroso, 2018). Increased flexibility in data analyses increases the rate of false positives and is more likely to produce results that researchers expect to find (Carp, 2012; Fanelli & Ioannidis, 2013; Ioannidis, 2005b; Ioannidis, Munafo, & Fusar-Poli, 2014; Simmons, Nelson, & Simonsohn, 2011). Conscious and unconscious manipulation of research data has been found in other areas of research (Simmons et al., 2011) and is at greater risk when topics are "hot" or controversial (Ioannidis, 2005b), such as ecstasy research.

Hill (1965) suggested that a causative relationship would be supported by consistent data across studies, times and place. This is not the case in ecstasy literature. As discussed above, studies reporting on the deficits associated with ecstasy use have been reporting smaller effect sizes over time (Taylor et al., 2011). This phenomenon has been seen in other areas of research (Ioannidis, 2005a), and may be attributed to hypercompetitive academic climates which promote the rapid dissemination of sensational discoveries early on.

Although Parrott et al. (2014) has claimed that "MDMA is certainly damaging" this opinion is based on observational research which cannot inform causation. Having a logical temporal relationship (i.e. deficits only come after ecstasy exposure) is supportive of a causal relationship. Most studies only look at cognitive function after exposure to ecstasy, which only demonstrates group differences rather than changes in an individual. The literature shows that in many studies the ecstasy using group had lower IQs than the control groups (Rogers et al., 2009), which has obvious confounds on neurocognitive performance. Likewise, ecstasy users often consume a larger variety of substances and in larger quantities than those in the comparison group.

Hill (1965) suggested that a casual relationship is more likely if a specific exposure is found to result in a specific outcome. Most studies find that ecstasy tablets sold on the street are impure or do not contain ecstasy at all (Palamar et al., 2017; Tanner-Smith, 2006; Saleemi et al., 2017; Vogels et al., 2009). Likewise, the deficits associated with ecstasy use are non-specific and represent a broad spectrum of problems (McGuire et al., 1994; Parrott, 2013).

Given the methodological issues and publication bias in this field of research the available evidence still only suggests that neurocognitive deficits found in ecstasy users are small and have little clinical relevance (Murphy et al., 2012; Nulsen et al., 2010; Roberts et al., 2016a; Rogers et al., 2009; Sumnall & Cole, 2005).

As early as 1977, the psychotherapeutic potential of MDMA was already understood by some psychologists and psychiatrists (Passie, 2018). However, investigations for its clinical use have been delayed since it was classified as a schedule I drug in 1985. This, in part, was propagated by sensational academic research which was biased towards documenting its harmful effects. In more recent years, the effects of MDMA have been studied more objectively examining both the potential for harm and possible clinical benefits in trials of MDMA-assisted psychotherapy (MDMA-AP). MDMA-AP has been shown to have efficacy in those suffering from posttraumatic stress disorder (PTSD) – a disorder that is often chronic and difficult to treat (Mithoefer et al., 2018, 2011; Oehen et al., 2012). Importantly, MDMA has been well tolerated in these trials with minimal occurrence of serious adverse events (Mithoefer et al., 2018, 2011; Oehen et al., 2012). Likewise, when scientifically rigorous methods (such as double-blind placebo control trials) are used to evaluate the safety of MDMA in healthy volunteers (n = 166) MDMA seems to be both physically and psychiatrically safe overall (Vizeli & Liechti, 2017).

Ideally, future research would be diverted away from poorly controled studies of ecstasy users and focused on controlled clinical trials of MDMA, as these can inform causal relationships. Furthermore, scientific journals should require that authors use precise language when describing their studies. If researchers are reporting on a sample of ecstasy users "MDMA" should not be used throughout the manuscript. Instead, MDMA should be mentioned in the introduction and/or discussion section as an ingredient often found in ecstasy. Also, titles and abstracts should not refer to the sample as "MDMA-users" if they are in fact poly-drug users with minimal exposure to ecstasy. Finally, the evidence that suggests MDMA can cause neurocognitive deficits is largely incomplete, inconsistent, and biased.

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Declaration of interest

None.

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