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COMMENTARY

MDMA and 5-HT neurotoxicity: the empirical evidence for its adverse effects in humans – no need for translation

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In this issue of the *BJP*, Green *et al.* suggest that animal data could not be used to predict the adverse effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans and that MDMA did not produce 5-HT neurotoxicity in the human brain. This proposal was, however, not accompanied by a review of the empirical evidence in humans. The neuroimaging data on 5-HT markers in abstinent recreational ecstasy/MDMA users are extensive and broadly consistent. Reduced levels of the 5-HT transporter (SERT) have been found by research groups worldwide using a variety of assessment measures. These SERT reductions occur across the higher brain regions and remain after controlling for potential confounds. There are also extensive empirical data for impairments in memory and higher cognition, with the neurocognitive deficits correlating with the extent of SERT loss. Hence, MDMA is clearly damaging to humans, with extensive empirical data for both structural and functional deficits.

LINKED ARTICLES

This article is a commentary on Green *et al.*, pp. 1523–1536 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2011.01819.x. A rebuttal by Green *et al.* also appears in this issue, pp. 1521–1522. To view this rebuttal visit http://dx.doi.org/10.1111/j.1476-5381.2012.01940.x

Abbreviations

fMRI, functional magnetic resonance imaging; IQ, intelligence quotient; MDMA, 3,4-methylenedioxymethamphetamine; SERT, 5-HT transporter

Green *et al.* (2012) suggested that animal laboratory research into 3,4-methylenedioxymethamphetamine (MDMA) provided evidence on the mechanisms for drug action, but did 'not allow accurate prediction of adverse events in humans'. Specifically, they questioned whether MDMA produced long-term 5-HT neurotoxicity in the human brain, stating that it was 'our contention that MDMA does not cause neurotoxic damage to 5-HT neurones in the human brain'; and later questioning 'whether MDMA alone produces long-term 5-HT neurotoxicity in the human brain'. I found these statements very surprising as there is an extensive body of empirical data demonstrating 5-HT deficits in abstinent Ecstasy/MDMA users. Green *et al.* (2012) also questioned whether MDMA produced functional deficits in humans, yet there is considerable empirical evidence for functional deficits as well. Acute MDMA administration can reduce neurocognitive test performance and alter functional magnetic resonance imaging (fMRI) parietal lobe activity. There are numerous studies showing long-term deficits in memory and higher cognition, and other psychobiological functions with a 5-HT component.

The first human neuroimaging studies of abstinent Ecstasy/MDMA users were conducted in the late 1990s. They indicated reduced 5-HT markers (including the 5-HT transporter SERT), with dopaminergic markers unchanged. Similar findings emerged in the early 2000s with different research groups. In a review of this neuroimaging literature, Reneman *et al.* (2006) concluded that 'the above-mentioned studies all have found reductions in SERT density in heavy ecstasy users with the use of different techniques and radioligands'. More

recently, Erritzoe *et al*. (2011) reported significantly lower SERT binding potential in the neocortex (–56%), pallidostriatum (–19%) and amygdala (–32%), with the extent of binding correlated with lifetime MDMA usage. Den Hollander *et al*. (2011) reported a significant reduction in hippocampal volume. Kish *et al*. (2010) compared 49 moderate Ecstasy/MDMA users with 50 non-user controls, with MDMA usage confirmed via hair analyses. Binding to SERT was significantly reduced in all the cerebral cortices and hippocampus, with group mean SERT reductions ranging from –19% to –46%. The degree of these reductions was significantly associated with the extent of past MDMA usage. The SERT deficits also correlated with the extent of memory task deficits. They investigated a range of other potential contributory factors, including gender, gene polymorphism and other psychoactive drug usage, and showed that the 5-HT deficits remained after controlling for every 'potential confound we could address'.

In relation to the functional consequences of recreational MDMA, Green *et al*. (2012) suggested that 'the evidence for impairment remains weak and controversial'. However, they noted that it was beyond the scope of their article to review the human functional literature. This is unfortunate as there is an extensive evidence for memory problems and other deficits. In Parrott (2006), I reviewed over 70 empirical papers that had found deficits in neurocognitive task performance and other psychobiological functions. They revealed deficits in retrospective memory, prospective memory, complex cognitive processing, problem solving and social intelligence. Since that review, increased rates of sleep apnoea have also been reported, as breathing control has a 5-HT component (McCann *et al*., 2009).

It is important, however, to note that many basic cognitive skills are not affected, and that there are also many reports of *unimpaired* functioning or only mild deficits. Several factors may modulate these changes, including lifetime usage, intensity of use and psychoactive co-drugs. Hence, it is important to note that these deficits remain after controlling for the influence of other psychoactive drugs; indeed, it has become a common practice for journal papers in this field to describe or control for the potential influence of other psychoactive drugs. Rogers *et al*. (2009) undertook a review of over 100 studies into the neuropsychobiological effects of recreational Ecstasy/MDMA. Six memory tasks and intelligence quotient (IQ) measures had been employed in sufficient studies for meta-analysis. On the memory tasks, MDMA users were significantly impaired in comparison with both non-user controls (alcohol drinkers) and polydrug user controls (cannabis and other illicit drug users). The only variable not to show this pattern was IQ, which did not differ between groups. It should also be noted that acute MDMA can damage neurocognition. In an event-related fMRI study, Ramaekers *et al*. (2009) reported that 75 mg oral MDMA increased prospective memory failures, and that the task deficits were associated with plasma MDMA levels. Furthermore, the memory problems were accompanied by fMRI changes in the parietal lobules and other brain regions.

Green *et al*. (2012) argued that given the large number of recreational users, there should be more evidence for Ecstasy-related problems. Again, several studies have addressed this question. Topp *et al*. (1999) interviewed more than 300 regular users, who reported an *average* of eight physical and four psychological problems attributed to Ecstasy. Montgomery *et al*. (2010) demonstrated the adverse practical consequences of the neurocognitive deficits for everyday performance skills using a virtual reality paradigm. In an Internet survey of 282 Ecstasy users, the incidence of drug-attributed problems was associated with lifetime usage (Parrott *et al*., 2002). While 19% of light Ecstasy users reported memory problems, this increased to 52% for moderate users and 73% for heavy Ecstasy users. This latter group complained of various ecstasy-attributed problems, including weight loss (43%), anxiety (60%) and depression (65%). There are many empirical reports of chronic psychiatric problems, including depression (review: Parrott, 2006), with Verheyden *et al*. (2003) noting that the majority of former Ecstasy users reported 'improved mental health' after quitting.

Green *et al*. (2012) suggested that MDMA might act as a neurotoxin to the human brain, but only under severe hyperthermia. In a recent review of the thermal effects of MDMA in humans (Parrott, 2012), MDMA was confirmed as a thermal stressor in both laboratory and field studies, although most recreational users experience moderate thermal stress. In one field study, we monitored 12 Ecstasy users before, during, and after their dance clubbing (Parrott *et al*., 2008), with MDMA presence biochemically confirmed in every 'on-Ecstasy' sample. The group mean peak thermal increase on-MDMA was +0.2°C, but this was accompanied by a group mean peak increase of more than 800% in saliva cortisol. This indicates the profound bioenergetic stress being caused by MDMA. Bioenergetic stress may indeed be central to the damaging effects of Ecstasy/MDMA (Parrott, 2006), helping to explain why MDMA is a 5-HT neurotoxin for moderate recreational users (see neuroimaging studies earlier). The bioenergetic stress model for humans is also congruent with animal models. Yamamoto *et al*. (2010) proposed that the underlying mechanisms for the neurotoxic effects of amphetamines and methamphetamines were multiple, but were focused around bioenergetic stress.

Finally, there is a current debate over the nature of the neurotransmitter system changes that underlie '5-HT neurotoxicity'. Biezonski and Meyer (2011) noted that 'most investigators in this field equate MDMA-induced reductions in serotonergic markers with a neurodegenerative process'. Indeed, this has been the predominant model since MDMA-induced neurotoxicity was first described in the mid-1980s, but other possible interpretations do not involve neurodegeneration. Despite this debate about the underlying mechanisms, Biezonski and Meyer (2011) were still able to conclude: 'Given the plethora of evidence showing the 5-HT- and SERT-depleting effects of MDMA, this substance can certainly be considered "neurotoxic" in terms of causing serotonergic dysfunction'. Whatever the underlying mechanisms for neurotoxicity, and despite species differences in pharmacokinetics, MDMA is clearly damaging to laboratory animals and humans.

Conflicts of interest

The author has no conflicts of interest to declare.

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