Addiction

COMMENTARY

Commentary on Halpern *et al.* (2011): Strengthening the case against functionally significant serotonergic neurotoxicity in human MDMA (ecstasy) users

Halpern and colleagues [1] have overcome some of the methodological issues raised previously [2] concerning their initial pilot study of ecstasy users [3]. Their latest study [1] found that of 15 neuropsychological tests tapping various cognitive and memory functions reported previously by others to differentiate ecstasy users from controls, only the Revised Strategy Applications Test (RSAT) showed a clear indication of poorer performance in heavy (but not moderate) ecstasy users compared to controls. Ecstasy users were selected for low exposure to other illicit drugs and alcohol, whereas in most other studies of this type the influence of potentially confounding associations between the use of ecstasy and other substances could not be ruled out entirely [4–7]. Further, the non-user controls recruited by Halpern *et al.* [1] were members of the 'rave' subculture like the ecstasy users, and the analyses adjusted for demographic and other factors [e.g. attention deficit hyperactive disorder (ADHD)] that might have also acted as confounds. For such reasons this may be the most informative retrospective study to date of cognition and memory in ecstasy users.

The finding of relatively poorer self-regulation as indexed by the RSAT in heavy users is interesting. Poor performance on the RSAT in brain-injured patients has been interpreted as possibly reflecting deficient prefrontal inhibitory control over reward-driven responding [8]. In non-brain-injured young adults, inherently low serotonergic functioning has been linked to impulsivity [9], which in turn has been associated with low prefrontal cortical activation [10] as well as elevated sensitivity to reward, signs of frontal lobe dysfunction in everyday life [11] and heavier substance use [9–11]. Given these associations, the finding of a recent prospective study that higher impulsivity on a neuropsychological test in ecstasy-naive individuals predicted subsequent ecstasy use [12] is not surprising. Reports of higher impulsivity and poorer executive cognitive functioning in heavy ecstasy users, as measured by tests such as the RSAT, are entirely consistent with pre-drug traits that promote increased substance use.

An impressive amount of research effort has been directed towards finding functional signs of serotonergic neurotoxicity in human ecstasy users, yet the evidence remains mixed [4–7,13]. By contrast, comparatively little research interest has been evident regarding the possible functional neurotoxic sequelae of another serotonin-releasing agent, fenfluramine. This drug has been known since the 1970s to cause chronic reduction of brain serotonin in laboratory animals at lower effective doses than 3,4-methylenedioxymethamphetamine (MDMA), yet was prescribed for weight loss in multiple daily doses to tens of millions of people world-wide before being withdrawn in 1997 due to evidence that it damages heart valves [14]. A recent brain imaging study [15] indicated deficiencies of serotonin transporters in people who had last taken fenfluramine years earlier; by contrast, such deficiencies in ecstasy users appear to recover with abstinence [16]. Those who took fenfluramine for weight loss daily over extended periods may be at least as likely to exhibit functional signs of serotonergic neurotoxicity as the sporadic users of MDMA at 'raves', yet for political reasons there has been far more interest in MDMA users than in fenfluramine users in this regard. However, even in the case of fenfluramine, an argument paralleling the one presented above concerning recreational MDMA use may be relevant: if inherently low serotonergic functioning is associated with greater likelihood of impulsive overeating, such that many such individuals were prescribed fenfluramine as an appetite suppressant, then long-term post-treatment signs of low serotonin activity and related cognitive or memory deficiencies could conceivably reflect pre-morbid characteristics rather than neurotoxic sequelae of drug exposure. These contrasting possibilities cannot be disentangled in retrospective studies. In the case of MDMA use, the very same traits of higher impulsivity, poorer executive control and mildly deficient serotonergic system functioning that have been attributed by some to serotonergic neurotoxicity may predispose to heavier drug/alcohol use even in people who have never taken MDMA; thus one would expect that the heaviest ecstasy users would, on average, be more impulsive even if there is no neurotoxicity at the doses taken by ecstasy users.

The obvious way to resolve this dilemma is via within-subjects comparison in human volunteers before versus after controlled experimental exposure to MDMA, an approach which in the limited examples to date has not indicated any resulting deficits [17,18]. Given that MDMA is being administered to human patients to assess its efficacy as a treatment for post-traumatic stress disorder [18], ethical arguments against an experimental within-subjects approach to detecting possible long-term brain, cognitive and memory effects of MDMA in human volunteers may now be less relevant. Once such research has been replicated consistently across a range of typical

dosing regimens, the chimera of MDMA-induced neurotoxicity in human ecstasy users may finally be put to rest. Until then, the well-designed study of Halpern *et al.* [1] has yielded findings supporting that outcome.

Declaration of interests

None.

Keywords Ecstasy, fenfluramine, impulsivity, MDMA, neurotoxicity, serotonin.

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