Addiction

Letters to the Editor

The journal publishes both invited and unsolicited letters.

RESIDUAL NEUROCOGNITIVE FEATURES OF ECSTASY USE: A RE-INTERPRETATION OF HALPERN *ET AL.* (2011) CONSISTENT WITH SEROTONERGIC NEUROTOXICITY

Halpern *et al.* [1] presented some interesting findings from a study of abstinent ecstasy users in Salt Lake City, USA. Their ecstasy group reported comparatively slight use of all psychoactive drugs, both legal and illicit, and were therefore different from the typical user who often takes a range of other drugs. Their control group comprised similar-aged occasional rave attendees, who had never taken ecstasy/3,4-methylenedioxymethamphetamine (MDMA) but had some slight use of other drugs. Halpern *et al.* [1] reported that 'we failed to demonstrate marked residual cognitive effects in ecstasy users', and in their Discussion they suggested that their findings 'might instead reflect correctly that illicit ecstasy use, by itself, does not generally produce lasting residual neurotoxicity'. I would like to present a rather different interpretation of their findings, as I believe that their data are consistent with current knowledge about the adverse cognitive effects of MDMA and its neurotoxic properties.

First, it should be noted that a number of previous studies have also found comparatively slight neurocognitive changes. In a comprehensive meta-analysis of the ecstasy and cognition literature, Rogers *et al.* [2] noted marked variation across studies. One of the tasks used by Halpern *et al.* [1] was digit span, and in the meta-analysis by Rogers *et al.* [2] their Figure 16 revealed a mixture of non-significant and significant changes, although the pooled data showed a significant overall impairment for ecstasy users compared to polydrug controls ($P = 0.017$). This same pattern emerged with many of the other cognitive tasks. For instance, with the composite index for verbal memory immediate recall (Fig. 21), several studies showed similar group means, others showed moderate significant impairments, while some showed more pronounced deficits. The pooled findings from the 27 published studies again showed a significant overall impairment, in comparison with polydrug control ($P < 0.001$). Rogers *et al.* [2] conducted a meta-analysis on seven dependent variables, and six of these showed significant deficits for ecstasy-exposed individuals: Rey Auditory Verbal Learning Test (RAVLT) immediate word recall, RAVLT delayed word recall, Rivermead Behavioural Memory Test (RBMT) immediate prose recall, RBMT delayed prose recall, digit span forwards and digit span backwards. The only measure where ecstasy users did not differ from controls was the National Adult Reading Test Intelligence Quotient (NART IQ) index, showing that the groups did not differ in basic intelligence (Table 4 in their reference 2).

So what is causing this variance in findings; why have some studies found cognitive deficits whereas others have not? This was the key issue I addressed in an earlier MDMA review paper [3]. In the introduction I noted that:

> 'Recreational Ecstasy/MDMA users can experience a range of neuropsychobiological problems. In particular, they have been found to display functional deficits in neurocognitive test performance, altered cognitive-emotional information processing, raised psychiatric symptom profiles, disordered sleep, sexual dysfunctions, altered EEG patterns, modified event-related potentials, reduced immuno-competence, increased oxidative stress, and other psychobiological changes (list of 79 refereed papers—see original article). However amongst this extensive body of empirical data, most studies have also found that some groups/types of Ecstasy user were not impaired, or displayed deficits on just a few measures. Hence this same literature provides extensive evidence for *unimpaired* neuropsychobiological functioning. The topic for this review is to examine some of the factors which may be contributing to this variance in findings'.

My main conclusion was that four key factors were important: life-time ecstasy/MDMA dosage, intensity of MDMA usage per session, environmental costimulation and other psychoactive drugs [3]. With reference to life-time dosage, when life-time MDMA usage was below 50 occasions, overall group performance was generally not significantly impaired, whereas above that level it was often significantly impaired (pp. 148–149). In this regard, the median usage for Halpern *et al.*'s overall group was 43.5 occasions/life-time. With reference to the intensity of MDMA usage, multiple use or 'bingeing' tends to be more damaging, than lighter intermittent use [4,5]. This factor is difficult to gauge in Halpern's participants, because ecstasy usage rates per session were not presented. However, their volunteers seem to be at the careful end of the drug-usage spectrum. Their self-reported attendance at raves had a median of 98 occasions, so given a life-time usage of 43.5 occasions, for

the majority of raves visits they were *not* on ecstasy. On these drug-free visits, they would not have experienced the 800% cortisol increase which occurs with dance-clubbers on MDMA, as cortisol levels remain unchanged when they go dance-clubbing off MDMA [6]. Turning to polydrug aspects, the volunteers in Halpern *et al.* [1] reported a median life-time 'alcohol intoxication' of 10 occasions/life-time (intoxication being defined as four alcoholic drinks within 4 hours). Their life-time use of cannabis was also comparatively slight (median 10 'intoxications' per life-time), and tobacco usage was minimal (cigarettes/day: median = 0; interquartile range = 0–0.3). Hence, the participants in Halpern *et al.* [1] seem to be relatively health-conscious, with relatively careful patterns of psychoactive drug usage.

However, despite their light drug usage, the ecstasy users in Halpern *et al.* [1] still displayed significant neurocognitive deficits. Their Table 2 listed the following tasks with significant impairments, relative to controls: Wechsler Memory Scale spatial span forwards ($P < 0.04$), Wechsler Adult Intelligence Scale digit-substitution substitution ($P < 0.02$), Wechsler Adult Intelligence Scale vocabulary score ($P < 0.01$), Wechsler Adult Intelligence Scale digits backwards ($P < 0.05$) and grooved pegboard non-dominant hand ($P < 0.02$). These findings agree with many previous reports of impaired cognitive performance in drug-free recreational ecstasy/MDMA users [7–18]. Hence, I would disagree with Halpern *et al.* [1] in their suggestion that: 'More probably, such differences report chance associations—a phenomenon to be fully expected, given that we performed multiple comparisons without formal statistical correction'. The Halpern battery contained several tasks which were unimpaired, although some of these were simple measures which are not typically affected by MDMA (e.g. trail-making A, their reference 13). The absence of deficits in tasks such trail-making B and California Word Learning was, however, more surprising, as these types of frontal executive tasks and verbal memory tasks are often impaired [13–20].

Halpern *et al.* [1] divided their sample into two subgroups, with moderate users defined as fewer than 50 life-time occasions, and heavy users defined as those with 50+ occasions. Against expectations, these two subgroups did not generally differ, and in some measures the moderate users were more impaired. Hence, they failed to replicate their earlier study [21], where only heavy ecstasy users showed significant impairments. The authors did note, however, that their heavier-user subgroup did not contain many heavy users—as only six of the 22 members of the heavy subgroup had taken MDMA on 150+ occasions. The life-time ecstasy usage rates for the two subgroups were also not presented, making their subgroup characteristics difficult to compare with other studies. Given a median usage for the overall sample of 43.5 occasions, the usage for their 'moderate' users would have been comparatively low. On the Revised Strategy Applications Test, Halpern *et al.* [1] reported a significant dose-related impairment, which was interpreted as indicating: 'Poorer strategic self-regulation and hence perhaps greater reflection impulsivity (i.e. insufficient information gathering before launching into the task)'. This finding was very similar to that originally reported by Morgan [22], using the Matching Familiar Figures test. The ecstasy users were more rapid in their initial response, but made more errors than both non-user controls and polydrug user controls, with Morgan noting that this indicated greater behavioural impulsivity in ecstasy users. The reduction in cognitive control agrees with many other findings of significant deficits in executive processing, frontal planning, social intelligence, prospective (future planned) memory, problem solving and other aspects of higher cognition [7,13,15,16,19,20].

One novel and intriguing finding was on the grooved pegboard test. With the dominant hand, performance was unimpaired, confirming that the two subgroups were similar in basic psychomotor intelligence [1]; yet with the non-dominant hand, ecstasy users were significantly slower than controls ($P = 0.02$). Furthermore, this deficit was dose-related, with heavy users being relatively more impaired ($P = 0.003$ versus controls). Halpern *et al.* [1] suggested that 'the more robust difference on the grooved pegboard with the non-dominant hand in heavy users (Table 3) was due probably to chance'. However, I believe it may reflect a far more interesting and meaningful deficit. As noted earlier, the types of neurocognitive problem associated with MDMA often involve higher integrative skills. Simple basic cognitive skills are generally unimpaired, whereas tasks involving higher cognitive control are often impaired [3,7,15,19,20]. With the dominant hand, the pegboard test requires simple over-learned psychomotor abilities; but when using the non-dominant hand, new unpractised skills come into play, and here higher cognitive control may become more important. Further ecstasy/MDMA studies with this intriguing measure would certainly seem warranted.

Turning to the question of serotonergic neurotoxicity, Halpern *et al.* [1] suggested that that their relatively 'modest' performance deficits may have been be due to other confounds, and that 'our findings indicate that the neurotoxicity of ecstasy use remains incompletely resolved' [note: median last ecstasy usage was 121 days, hence their findings are pertinent for the question of enduring toxicity]. There are, however, many neuroimaging studies which have found significant serotonergic deficits. In a review of this neuroimaging literature, Cowan [23] concluded that the most robust finding was a reduction in serotonin transporter (SERT) density. That review included several large studies, including those by

McCann's group in the United States, Reneman's group in the Netherlands, Buchert's group in Germany and others. In a recent Canadian study, Kish *et al.* [13] has again confirmed extensive serotonergic neurotoxicity. In a comparison of 49 abstinent ecstasy users with 50 non-user controls, SERT binding was reduced significantly in every region of the cerebral cortex (reductions ranging from –19% to –46%) and hippocampus (–21%). These SERT reductions were associated statistically with cumulative life-time MDMA usage and maximum single-occasion use. These serotonergic deficits also remained after controlling for a wide range of potential confounds, including other psychoactive drug use. They also correlated significantly with various aspects of cognitive performance. This agrees with McCann *et al.* [10], who had earlier reported significant correlations between reduced SERT binding and neurocognitive deficits. In a functional magnetic resonance imaging (fMRI) study of adolescent ecstasy users, Jacobsen *et al.* [24] reported abnormal function of the left hippocampus during performance of a high-load working memory task. In an event-related potential study, Burgess *et al.* [25] showed that ecstasy users had a significantly reduced late-positive response in the left parietal cortex during performance of a word recognition task. These are just a selection of the empirical reports showing modified neural activity and/or neurocognitive changes.

In conclusion, Halpern *et al.* [1] argued that the cognitive deficits they observed were relatively modest, and this supported the notion that MDMA was not really neurotoxic. I would like offer a completely different interpretation, and argue that their modest cognitive deficits are entirely congruent with current understandings about MDMA. In the bio-energetic stress model [3,8], MDMA is seen as most damaging when taken intensively and cumulatively, and least damaging when taken intermittently and with minimal co stressors. The participants in Halpern's study seem to have been relatively careful in their usage of MDMA, with life-time rates which were not high, consumption patterns which were occasional rather than intensive, and with very limited use of other drugs. Yet even under these neuroprotective circumstances, Halpern and colleagues have shown that that MDMA is cognitively damaging. Far from refuting MDMA neurotoxicity, Halpern *et al.* [1] have confirmed its potential for causing neurobiological damage, even when taken carefully.

Keywords Cognition, ecstasy, executive function, MDMA, memory, neurotoxicity, serotonin.

ANDREW C. PARROTT
Department of Psychology, Swansea University, Swansea, Wales SA2 8PP, UK.
E-mail: a.c.parrott@swansea.ac.uk

References

1. Halpern J. H., Sherwood A. R., Hudson J. I. , Gruber S., Kozin D., Pope H. G., Jr. Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. *Addiction* 2011; **106**: 777–86.
2. Rogers G., Elston J., Garside R., Roome C., Taylor R., Younger P. *et al.* The harmful health effects of recreational ecstasy: a systematic review of observational evidence. *Health Technol Assess* 2009; **13**: 1–315.
3. Parrott A. C. MDMA in humans: factors which affect the neuropsychobiological profiles of recreational Ecstasy users, the integrative role of bio-energetic stress. *J Psychopharmacol* 2006; **20**: 147–63.
4. Topp L., Hando J., Dillon P., Roche A., Solowij N. Ecstasy use in Australia: patterns of use and associated harm. *Drug Alcohol Depend* 1999; **55**: 105–15.
5. Parrott A. C. Chronic tolerance to recreational MDMA (3,4 methylenedioxymethamphetamine) or ecstasy. *J Psychopharmacol* 2005; **19**: 71–83.
6. Parrott A. C., Lock J., Conner A. C., Kissling C., Thome J. Dance clubbing on MDMA and during abstinence from Ecstasy/MDMA: prospective neuroendocrine and psychobiological changes. *Neuropsychobiology* 2008; **57**: 165–80.
7. Fox H. C., McLean A., Turner J. J. D., Parrott A. C., Rogers R., Sahakian B. J. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ('ecstasy') polydrug users. *Psychopharmacology* 2002; **162**: 203–14.
8. Parrott A. C. Cortisol and MDMA (3,4-methylenedioxyme thamphetamine): neurohormonal aspects of bioenergetic-stress in Ecstasy users. *Neuropsychobiology* 2009; **60**: 148–58.
9. McCann U. D., Mertl M., Eligulasvili V., Ricaurte G. A. Cognitive performance in (+—) 3,4-methylenedioxymethampheta mine (MDMA, 'Ecstasy') uses: a controlled study. *Psychopharmacology* 1999; **143**: 417–25.
10. Mc Cann U. D., Szabo Z., Vranesic M., Palermo M., Mathews W. B., Ravert H. T. *et al.* Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/–)3,4-methylenedioxymethamphetamine ('ecstasy') users: relationship to cognitive performance. *Psychopharmacology* 2008; **200**: 439–50.
11. Rodgers J. Cognitive performance amongst recreational users of 'ecstasy'. *Psychopharmacology* 2000; **151**: 19–24.
12. Quednow B. B., Jessen F., Kuhn K. U., Maier W., Daum I., Wagner M. Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. *J Psychopharmacol* 2006; **20**: 373–84.
13. Kish S. J., Lerch J., Furukawa Y., Tong J., McCluskey T., Wilkins D. *et al.* Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study. *Brain* 2010; **133**: 1779–97.
14. Wareing M., Fisk M., Murphy J. E. Working deficits in current and& previous users of MDMA ('ecstasy'). *Br J Psychol* 2000; **91**: 181–8.
15. Montgomery C., Hatton N. P., Fisk J. E., Ogden R. S., Jansari A. Assessing the functional significance of ecstasy related memory deficits using a virtual reality paradigm. *Hum Psychopharmacol* 2010; **25**: 318–25.
16. Rendell P. G., Gray T. J., Henry J. D., Tolan A. Prospective

memory impairment in 'ecstasy' (MDMA) users. *Psychopharmacology* 2007; **194**: 497–504.
17. Morgan M. J. Memory deficits associated with recreational use of 'ecstasy' (MDMA). *Psychopharmacology* 1999; **141**: 30–6.
18. Zakzanis K. K., Campbell Z. Memory impairment in now abstinent MDMA users and continued users: a longitudinal follow-up. *Neurology* 2006; **66**: 740–1.
19. Reay J. L., Hamilton C., Kennedy D. O., Scholey A. B. MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgement processes. *J Psychopharmacol* 2006; **20**: 385–8.
20. Fisk J. E., Montgomery C., Wareing M., Murphy P. N. Reasoning deficits in ecstasy (MDMA) polydrug users. *Psychopharmacology* 2005; **181**: 550–9.
21. Halpern J. H., Pope H. G., Sherwood A. R., Barry S., Hudson J. I., Yurgelun-Todd D. Residual effects of illicit 3,4-methylenedioxymethamphetamine in individuals with minimal exposure to other drugs. *Drug Alcohol Depend* 2004; **75**: 135–47.
22. Morgan M. J. Recreational use of 'ecstasy' (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology* 1998; **19**: 252–64.
23. Cowan R. L. Neuroimaging research in human MDMA users: a review. *Psychopharmacology* 2007; **189**: 539–6.
24. Jacobsen L. K., Mencl W. E., Pugh K. R., Skudlarski P., Krystal J. H. Preliminary evidence of hippocampal dysfunction in adolescent MDMA ('ecstasy') users: possible relationship to neurotoxic effects. *Psychopharmacology* 2004; **173**: 383–90.
25. Burgess A. P., Venables L., Jones H., Edwards R., Parrott A. C. Evidence for selective impairments of verbal recollection in abstinent recreational users of methylenedioxymethamphetamine ('ecstasy'). *Psychopharmacology* 2011. Epub ahead of print 10 March.

COMMENT ON HALPERN *ET AL.* (2011)

The study by Halpern and co-workers [1] published recently in this journal reports findings in which ecstasy users with modest use of other drugs did not exhibit deficits on the majority of measures that were administered. This paper may be criticized on a number of grounds, but our focus here will be on two main areas: the nature of the sample and the choice of measures that were administered.

First, as the authors acknowledge, the sample is not representative of typical ecstasy/polydrug users. While the stated rationale for this choice has its merits, clearly it limits the generalizability of any inferences that might be drawn. More specifically, relatively heavy users of ecstasy are not well represented in Halpern *et al.*'s sample. Furthermore, the absence of an ecstasy-related deficit on many of the measures does not give ecstasy a clean bill of health (as the authors acknowledge), as the restriction on the use of other drugs reduces the possibility of detecting cocktail effects in which ecstasy may interact with other drugs such as alcohol, producing both acute and more longer-lasting deficits [2].

The second criticism of Halpern *et al.*'s study involves the choice of measures that were used. First, as in many studies concerning illicit drug use the tests administered were not informed by current theoretical perspectives in cognitive psychology. Many of the measures that are commonly used were developed for use with clinical groups and often lack the sensitivity to detect the subtle deficits present in recreational drug users. Furthermore, it is not surprising that many of the measures administered by Halpern *et al.* failed to reveal ecstasy-related deficits because these measures have failed to do so in the past. For example, four of five studies utilizing the Trail-Making Test Part B (TMT-B) revealed no statistically significant differences (the remaining one yielding ambiguous results) [3]. Furthermore, a recent review of the literature [4] has demonstrated that, in relation to the Wisconsin Card Sorting Test (WCST) and the Stroop test, the majority of studies have failed to reveal ecstasy-related deficits; and only half of those studies using the F, A and S letter variant of the verbal fluency paradigm reported statistically significant ecstasy-related deficits. It is worthy of note that a more demanding task, Chicago word fluency, has been found to be associated with ecstasy-related deficits. The same review [4] has also shown that the majority of studies using simple spatial span or Corsi block tapping also failed to reveal ecstasy-related deficits.

Utilizing recent perspectives from cognitive psychology, in a number of studies [5,6] we have demonstrated that ecstasy/polydrug users are selectively impaired in executive pre-frontal tasks which require the updating of the contents of the working memory system. Other executive component processes which require the switching of attention (e.g. as assessed by the TMT-B and the WCST) or the inhibition of pre-potent responses (the Stroop) appear to be spared. Thus, in closing, we would argue that Halpern *et al.*'s results were not entirely unexpected. However, the implications of their findings are perhaps rather limited.

Declarations of interest

None.

JOHN E. FISK[1], PHILIP N. MURPHY[2], CATHARINE MONTGOMERY[3] & MICHELLE WAREING[4]
School of Psychology, University of Central Lancashire, Preston PR1 2HE, UK[1], *Department of Social and Psychological Sciences, Edge Hill University, Ormskirk, Lancashire L39 4QP, UK*[2,4] *and School of Natural Sciences and Psychology, Liverpool John Moores University, Liverpool L3 3AF, UK*[3].
E-mail: jfisk@uclan.ac.uk