

published studies in the field. A review of this literature appears to indicate that there is comprehensive and robust evidence suggesting that, at least for some users, ecstasy may confer cognitive risk. It is therefore disappointing that papers such as this indicate that perhaps the field has not moved on from simply asking 'does ecstasy have negative consequences?'. We would hope that a more sophisticated approach which asks 'if ecstasy use can be problematic what are the risk factors and who is most vulnerable?' would be a timely and more appropriate use of expertise and resources.

In summary, it is our view that the conclusions drawn from the study published by Halpern *et al.* are misleading and do not fully acknowledge the significant limitations of their analyses in relation to the low statistical power and therefore potentially misleading the reader.

Declarations of interest

None.

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REPLY TO PARROTT (2011), FISK ET AL. (2011) AND RODGERS ET AL. (2011)

In the first of the three letters above, Professor Parrott [1] raises several points regarding our recent study of abstinent ecstasy users, in which we found little evidence of cognitive deficits in these individuals compared to otherwise similar non-users [2]. We agree with some, but not quite all, of Parrott's points, as follows.

Modest levels of ecstasy exposure

Parrott suggests that our largely negative findings might reflect relatively 'careful' patterns of ecstasy use in our participants compared to participants in other studies. Indeed, we acknowledge this possibility in our own discussion, where we note that only six of our 52 ecstasy users reported extremely high levels of exposure (≥ 150 life-time episodes of ecstasy use). Nevertheless, we would note that our ecstasy users reported rates and amounts of exposure comparable to the studies reviewed in the meta-analysis by Zakzanis *et al.* [3] cited in Dr Rodger's letter (see below). One might envisage that levels of use higher than these, especially 'bingeing' with very large numbers of pills on a single occasion, could cause greater toxicity. However, when we performed exploratory analyses comparing our 15 heaviest 'bingers' (a minimum of six pills on a single occasion) to our 59 non-users, we found no obvious trends towards greater deficits on the major outcome measures (those shown in our Table 4), although these exercises had limited statistical power.

Behavioral or reflection impulsivity

Parrott notes, as do we in our own discussion, that our findings of dose-related impairment in strategic self-regulation among ecstasy users are in accord with many other studies of ecstasy users. We again agree, but we reiterate our caution that this finding might not represent an *effect* of ecstasy, as impulsivity might well predispose individuals to use ecstasy more frequently.

Other significant differences between users and non-users

We acknowledge that we found several differences of modest significance between users and non-users on our Table 2, but as noted in our paper we are particularly hesitant to ascribe these to ecstasy, as these differences were confined largely to the moderate users rather than the heavy users—a finding inconsistent with a hypothesis of dose-related ecstasy-induced neurotoxicity. Therefore, we continue to caution that these might be chance findings, especially when one considers the large number of comparisons for statistical analysis, together with the fact that most of these differences barely exceeded the 0.05 level of statistical significance.

Performance on the grooved pegboard with the non-dominant hand

One exception to our previous comment was non-dominant performance on the grooved pegboard, which reached an alpha of 0.003 in the comparison of heavy users versus non-users (our Table 3)—favoring Parrott's hypothesis that this finding might represent a real, rather

than chance, phenomenon. We pursued this finding by assessing the association between log-transformed lifetime ecstasy use and pegboard time, using linear regression with adjustment for age, race/ethnicity and gender. This result was less impressive [coefficient (95% confidence interval) 4.3 (−0.2, 8.7) seconds of increased time on the pegboard for each increase of 1 in natural logarithm of life-time ecstasy use; $P = 0.06$]—but this finding may deserve further exploration.

The verdict?

Parrott concludes with a brief mention of the evidence suggesting serotonergic neurotoxicity in ecstasy users—and we have cited several reviews of this same evidence in our own paper. These biological studies, combined with the results of many previous field studies of ecstasy users, collectively favor that hypothesis that ecstasy may cause neurotoxicity (although recognizing that ‘neurotoxicity’ has no universally accepted definition). However, a recent prospective human study failed to show decreases in serotonin transporter (SERT) binding after 3,4-methylenedioxymethamphetamine (MDMA) use [4], and one longitudinal study of active users observed an increase in SERT over 2 years [5]. Also, it is possible that findings of apparent neurotoxicity in some other studies might be attributable to pre-existing factors or life-style factors found more often in ecstasy users, such as sleep deprivation [6]—a confounding factor not controlled for in most studies. Weighing these considerations together with the issues raised in several of our paragraphs above, we disagree with Parrott’s final sentence suggesting that our study has *confirmed* the potential of ecstasy to do cognitive damage.

Turning to the comments of Fisk *et al.* [7], we acknowledge the possibilities (i) that other illicit drugs might act synergistically with ecstasy to produce toxic effects not seen with ecstasy alone or (ii) that ecstasy might affect specific cognitive functions not tapped by our battery of 15 cognitive tests. Although both these possibilities are certainly plausible, we submit that they require further exploration and replication before they can be regarded as established.

Finally, looking at the comments of Rodgers *et al.* [8], these authors cite a meta-analysis [3] examining the effect of ecstasy on various cognitive measures that found a median standardized effect size of 0.33 for those effects that were significantly different from zero (suggesting that for all effects evaluated, the median would be even smaller). Rodgers *et al.* note that we would have only a 40% chance of detecting an effect size of this magnitude with our study sample. This is all mathematically legitimate, but neither the meta-analysis nor our own study can tell us whether these small effect sizes

reflect clinically important differences. Specifically, the standardized effect size is defined as the mean difference between two groups divided by the pooled standard deviation of the two groups. However, there is little consensus as to what mean difference is clinically important for the measures in these studies. Furthermore, even if we had consensus on the clinical significance of the mean differences, combination with the standard deviation makes interpretation even more difficult, because standard deviation may reflect the heterogeneity of the population, as well as the precision of measurements, over and above the clinical significance of a given difference. Thus, standardized effect size alone does not allow us to judge the clinical importance, or lack of importance, of ecstasy’s effects—and regrettably neither our study, nor even a meta-analysis of many studies, addresses this critical scientific issue squarely. Simply stated, our study does not rule out a clinically important toxic effect of ecstasy, but others studies do not rule it in, either. It should also be remembered that field studies of ecstasy users are inevitably subject to numerous confounders, the majority of which might be expected to bias findings away from the null, as we have noted in our paper. Thus, one must exercise great care in interpreting the clinical significance of findings with small effect sizes, given that some of the putative effect may reflect confounders that have not been controlled for adequately.

We also acknowledge the possibility of prospective memory deficits, as raised by these authors. However, the paper that they cite is a web-based survey looking at self-reports—a design potentially vulnerable to selection bias, reporting bias and confounding factors. Moreover, two laboratory-based studies of ecstasy users [9,10] failed to find evidence of ecstasy-associated prospective memory performance (although one [10] found some deficits on retrospective memory). Therefore, it is premature to regard findings of prospective memory deficits from ecstasy use as established.

In conclusion, we note that the letter-writers often seem to rely upon past research studies that are potentially vulnerable to the very confounding factors that our study was designed to overcome. By themselves, therefore, such past reports would seem insufficient to refute our findings. Instead, if we are to advance our understanding of the effects of ecstasy, the field will need future studies with even more rigorous designs to minimize confounding effects.

Of course, we share the opinions of all three letter-writers that it is clearly inappropriate to jump to the conclusion that ecstasy is safe; but it is also inappropriate, at this stage of knowledge, to imply that ecstasy is invariably neurotoxic to a clinically significant degree in all types of users. We submit that the quality of past data, with its

many methodological limitations, does not justify that level of certainty.

Declarations of interest

None.

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