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'ECSTASY USE, BY ITSELF, DOES NOT RESULT IN RESIDUAL NEUROTOXICITY' – A POWERFUL ARGUMENT?

We read with interest the paper published in this journal by Halpern and colleagues [1], which reported findings from a study examining cognitive function in ecstasy/3,4-methylenedioxymethamphetamine (MDMA) users. The authors conclude that they had failed to demonstrate 'marked residual cognitive effects in ecstasy users' and they suggest that their data may indicate that ecstasy use, by itself, does not result in 'residual neurotoxicity'. The publication of this paper has resulted in significant press coverage in the United Kingdom, including a report in the *Guardian* newspaper which concludes that 'There is no evidence that ecstasy causes "brain damage" ' [2]. Given the prevalence of ecstasy use, a well-designed and credible study that demonstrated no long-term sequelae would indeed be very welcome; however, we have significant concerns about the study, the conclusions drawn and the subsequent over/misinterpretation of the findings by the popular media, which may mislead the public into assuming that ecstasy can be used without risk.

A key objection to Halpern *et al.*'s conclusion concerns the statistical power of the study and the effect sizes expected for the impact of ecstasy use on cognitive function. Halpern *et al.* present the maximum effect size that their design could exclude for each measure tested (i.e. they could say confidently that if an effect of that magnitude existed then their design would find it). They report that 'we could exclude even a medium effect (Cohen's $d \geq 0.5$) on many cognitive measures' (p. 106). The problem here is that the typical effect sizes reported in previous research are lower than their threshold of likely detection. For example, Zakzanis *et al.* (2007) [3] conducted a meta-analysis of 35 empirical comparisons of the effects of ecstasy use on multiple domains of cognitive function. They present effect sizes (Cohen's *d* adjusted for sampling bias) for each of these domains. For those cognitive domains where the effect size was significantly different to zero, the majority were below the magnitude $d \geq 0.5$ that Halpern *et al.* were confident of detecting (for learning and memory, $d = -0.55$; for verbal comprehension, $d = -0.36$; for processing speed, $d = -0.33$; for attention and concentration, $d = -0.27$; for executive function, $d = -0.26$; Zakzanis *et al.* 2007 [3], p. 431). Therefore, Halpern *et al.*'s design was not capable of detecting the effects found typically in similar research because their sample size was too small. The median value for the effect sizes Zakzanis *et al.* reported as significantly different from zero was –0.33. The Halpern *et al.* study had two groups ($n = 59$ and $n = 52$). Using power analysis package G*Power 3 to determine *post-hoc* achieved power for the Halpern study, based on an independent-samples *t*-test comparing the groups' achieved power was found to be only 0.405.

That is, if comparing the two groups directly with this (typical) magnitude of effect size and these numbers of participants, Halpern *et al.* had only a 40.5% chance of finding a significant difference between the groups should one actually exist. Their design simply does not have sufficient statistical power to detect effects of the magnitude found typically in comparisons of cognitive function between ecstasy users and non-users and is at significant risk of type II error.

It is also curious that having developed such an extensive test battery the authors downplay the significant differences that are detected between the groups on a variety of cognitive tasks, including memory, vocabulary and fine motor skills. The fact that the authors managed to detect significant differences on any measures despite very low statistical power indicates that these effects are real and important and should not be diminished.

It is also interesting to note that Halpern *et al.*'s paper makes no reference to the growing body of research into ecstasy-related memory deficits within a real-world context, such as prospective memory (PM) deficits. Given the expanding evidence base within this domain, including the observation that PM deficits persist after statistically controlling for other drug use [4], it would appear remiss of the authors to have excluded such research.

Research into the putative impact of ecstasy use is extensive, with many hundreds, if not thousands, of

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

