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The preliminary study by Halpern et al. (2004) is a commendable attempt to isolate correlates of Ecstasy use from some of the many confounds that have plagued previous work on this controversial issue. However, Halpern et al. go far beyond their data by concluding that the few significant differences they found - out of a great number of comparisons conducted on a small sample of subjects - actually represent "residual neuropsychological effects of MDMA." Indeed, as their findings fail to establish a cause-effect relationship between heavy MDMA use and neurocognitive impairment, their use of the term "residual effect" is very misleading.

There are several serious problems with the Halpern et al. (2004) report. First, their analyses were statistically unsound. They obtained scores on 39 separate measures from only 39 subjects (even fewer in the case of the RSAT measures) and then subjected those scores to 117 between-group comparisons. Two basic rules of inferential statistics were thus violated: (1) There were as many measures as there were subjects, a situation likely to lead to artefactual or meaningless results (Tabachnik & Fidell, 2001, p. 117). Of the 9 comparisons out of 117 that were termed "significant" (most of which disappeared after additionally adjusting for family of origin), most compared 11 heavy users to 16 non-users; the comparisons on the two RSAT measures involved only 9 heavy users. (2) There was no correction for the inflated probability of making a Type I error due to the large number (117) of between-group comparisons. If an uncorrected alpha of p =.05 is used, 6 comparisons should show up as "significant" due to chance alone (.05 X 117). The simplest alpha correction would be .05/117 which yields a critical alpha level of p = .00004, but this significance level was not reached by any of their so-called "significant" findings. The authors' failure to adjust for Type I error seems incongruous with their previous studies (e.g. Pope et al., 2001; Pope et al., 2002) in which similar analyses were conducted. In these previous studies the authors set the alpha level at .01 "to provide some correction for the multiple comparisons" (Pope et al., 2002 p.305). In short, the data analysis looks somewhat like a fishing expedition that yielded very little (if anything) that can be justified on statistical grounds. To their credit, Halpern et al. did acknowledge the alpha inflation problem in their paper, but at the same time did nothing to correct it (ie., by adjusting the

alpha level), and instead make general conclusions about the differences between heavy and non-user groups "on a range of measures".

Another problem concerns their report of "significantly" poorer performance of heavy Ecstasy users than non-users on the WCST measure, categories completed (CC) and their assertion of a negative relationship between CC scores and lifetime Ecstasy use. Examination of the scatterplot (Figure 2-d) suggests that the distribution of CC scores in relation to the log of episodes of Ecstasy use is essentially flat except for a single, extreme outlier. Removal of that outlier would surely yield a trivially small R^2, a possibility that was acknowledged by Halpern et al. Lyvers also wondered whether the mean CC score in heavy users was actually "poor" in any meaningful sense. So he took a WCST study at random from his files (Stuss et al., 2000) and looked at the mean CC score in their control sample of 16 normal, non-brain-injured participants; to his surprise, the mean CC score was 7.5, essentially the same as the mean CC score of Halpern et al.'s (2004) supposedly "frontal-lobe-damaged" heavy Ecstasy users ($\underline{M}$ = 7.4). Halpern et al. reported that their 16 non-user controls scored 8.9 categories and the difference was significant at p = .05; however, in studies of frontal lobe injured patients, poor scores on CC are usually attributed to the high rate of perseverative errors (PE), as PE (especially if calculated as a percentage of total errors; Mountain & Snow, 1993) is the WCST measure that is most sensitive to frontal lobe dysfunction. Yet in Halpern et al.'s report, after adjusting for covariates there was no difference on PE between heavy Ecstasy users and controls, thus Halpern et al.'s general conclusion that the heavy users in their study showed signs of frontal lobe dysfunction due to neurotoxic effects of MDMA would seem unwarranted. Lyvers has found statistically significant effects of a low-to-moderate dose of alcohol (Lyvers & Maltzman, 1991), methadone withdrawal (Lyvers & Yakimoff, 2001), and even a single cigarette (Lyvers et al., 1994) on PE, hence this measure is sensitive to acute and residual drug effects as well as frontal lobe injury, and therefore should have yielded an effect in Halpern et al.'s study if their heavy Ecstasy users really did suffer residual effects of MDMA on frontal lobe functioning. But animal studies using rats or monkeys have failed to find any cognitive impairment associated with extreme

MDMA overdoses that permanently depleted more than 50% of brain serotonin (eg., Taffe et al., 2002), yet in lesion studies monkeys that suffered direct frontal lobe lesions display perseveration and other signs of cognitive impairment that resemble frontal lobe syndromes in humans (Dias et al., 1996). Because the animal evidence to date does not indicate that the serotonergic deficit following repeated exposure to massive doses of MDMA is accompanied by cognitive impairment, the claim that any cognitive deficits associated with heavy Ecstasy use in humans are attributable to serotonergic neurotoxicity appears untenable. Moreover, recent brain imaging studies comparing recent vs. former Ecstasy users indicate thatapparent serotonergic deficits observed in heavy Ecstasy users are reversible after an extended period of abstinence (Buchert et al., 2003; Reneman et al., 2001; Thomasius et al., 2003), suggesting that the extreme dosing regimens necessary to produce serotonergic neurotoxicity in laboratory animals are not relevant to human use of MDMA, as others have argued on different grounds (Aghajanian & Lieberman, 2001; Cole et al., 2002). Additionally, serotonergic deficits (eg., reduction in serotonin transporter densities) are also well-known effects of chronic antidepressant therapy with tricyclics and SSRIs (Grob, 2000) and may reflect brain changes associated with the therapeutic effects of such drugs, rather than neurotoxicity.

Assuming that Halpern et al. conduct further analyses on an appropriately large sample, controlling for subject-related confounding variables and adjusting for alpha inflation, and assuming that evidence of higher impulsivity and poorer "frontal lobe" executive cognitive functioning (as measured by WCST, RSAT and Stroop test) in heavy Ecstasy users remains statistically significant, would such findings then show that heavy use of Ecstasy causes residual cognitive impairment? Unfortunately the answer is NO. An impressive body of evidence to date has revealed that pre-drug impulsivity and executive cognitive deficits, often attributed to inherited deficiencies of the serotonergic system innervating the frontal lobes, strongly predispose to heavy use of alcohol or illicit drugs (eg., Cloninger, 1987; Conrod et al., 1997; Giancola et al., 1996; Higley & Linnoila, 1997; LeMarquand et al., 1998; Nielsen et al., 1998; Pihl et al., 1995; Tarter et al., 1995; Virkkunen & Linnoila, 1997). Thus young people who choose to use Ecstasy heavily are likely to differ from

moderate users or non-users in exactly these respects (impulsivity, executive cognitive functioning) *even before they ever tried Ecstasy*. Halpern et al.'s (2004) heavy Ecstasy users reported little use of alcohol or other drugs besides Ecstasy, but the mere fact that Ecstasy was their particular substance of choice does not eliminate this crucial confound. For example, trait impulsivity has been reported to be highly correlated with the intensity of euphoria induced by acute doses of cocaine (Cascella et al., 1994), thus it is not unreasonable that a similar relationship might occur for MDMA. If such a relationship between impulsivity and MDMA-induced euphoria exists, as it apparently does for cocaine, this would likely lead more inherently impulsive individuals who try MDMA to subsequently use MDMA more heavily than their less impulsive MDMA-using (or non-using) peers. Such a self-selection process would eventually yield groups of heavy Ecstasy users that on average are more impulsive and exhibit poorer executive cognitive functioning (correlated with impulsivity) than moderate users or non-users. In our view this is likely to be the case irrespective of whether the drug of choice is alcohol, cocaine, or Ecstasy. If such a self-selection process does occur - as seems increasingly likely based upon a large bodyof evidence such as that cited above - then the conclusion that observed differences in executive cognitive functioning and impulsivity between heavy users and moderate users or non-users must necessarily reflect "residual effects" of a particular drug (or drugs) becomes highly questionable unlessaccompanying physical signs of enduring drug-induced frontal lobe or other brain damage are actually observed – as is the case for chronic alcoholism and chronic cocaine or heroin addiction (see Lyvers, 2000), but not for heavy Ecstasy use (as noted above). The only way to get around this problem is to conduct dose-response trials of MDMA in human volunteers, but the few preliminary studies that have used this approach to date have found no enduring (ie, one month) effect of MDMA on brain imaging markers of the serotonergic system (Vollenweider et al., 2001) nor on measures of cognitive performance (Ludewig et al., 2001), though findings thus far are only generalizable to relatively low levels of MDMA exposure and did not employ a wide range of measures.

A relatively minor quibble with Halpern et al.'s (2004) report is thatthey continually refer to "MDMA users" when some samples of Ecstasy in the US contain little or no MDMA, often instead containing drugs that in high doses have been shown to be neurotoxic in laboratory animals, such as ketamine, dextromethorphan (see Olney et al., 1991, on NMDA antagonist neurotoxicity) or methamphetamine (see Ricaurte et al., 2003). For this reason it is perhaps more accurate to refer to these subjects as "Ecstasy users" rather than "MDMA users."

We have a few suggestions for Halpern et al. if they are to continue their work using a much larger sample. First, we suggestconduct ing two trials of WCST, with verbal instructions revealing the proper sorting strategy on the second trial; this approach renders the WCST more sensitive to frontal lobe dysfunction (Stuss et al., 2000) as well as drug effects (Lyvers & Maltzman, 1991; Lyvers et al, 1994; Lyvers & Yakimoff, 2001). We further suggest that Halpern et al. use the percent PE score as their criterion WCST measure because percent PE is the WCST measure most likely to correlate with frontal lobe dysfunction (Mountain & Snow, 1993). Finally, the abstinence period Halpern et al. (2004) required for their Ecstasy users was too short (10 days) given that animal studies, as well as thehuman brain imaging studies cited above, suggest that at least one month post-MDMA is necessary for serotonin function to fully recover from non-neurotoxic doses of MDMA. In order to avoid the confounding effect of short-term reversible serotonin depletion or transporter downregulation etc. as opposed to true neurotoxicity, an abstinence period of at least one month is in order. We hope this somewhat weak pilot study is only the first in a series of longitudinal studies, similar to the authors' work on cannabis, which will address these issues.

In conclusion, the preliminary findings of Halpern et al. (2004), though statistically unsound, are consistent with a large body of evidence to date showing strong associations between heavy drug use and inherent pre-drug traits such as impulsivity and executive cognitive dysfunction. For that reason alone, we hope Halpern et al. are able to expand their study to include an appropriately large sample. However, we do not accept that their findings demonstrate any residual effects of MDMA in heavy Ecstasy users, for the reasons outlined above.

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