Commentary.

Residual neurocognitive features of Ecstasy use: a reinterpretation 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/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, since I believe that their data are consistent with current knowledge about the adverse cognitive effects of MDMA, and its neurotoxic properties.

Firstly it should be noted that a number of previous studies have also found comparatively slight neurocognitive changes. In a comprehensive meta-analyses 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 (Figure 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 meta-analysis on seven dependent variables,

and six of these showed significant deficits for ecstasy exposed individuals: RAVLT immediate word recall, RAVLT delayed word recall, RBMT immediate prose recall, RBMT delayed prose recall, digit span forwards, and digit span backwards. The only measure where Ecstasy uses did not differ from controls was the NART IQ index, showing that the groups did not differ in basic intelligence (Table 4 in ref: 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: lifetime Ecstasy/MDMA dosage, intensity of MDMA usage per session, environmental co-stimulation, and other psychoactive drugs (3). With reference to lifetime dosage, when lifetime 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/lifetime. 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, since 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 lifetime 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, since 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 lifetime 'alcohol intoxication' of 10 occasions/lifetime (intoxication being defined as four alcoholic drinks within four hours). Their lifetime use of cannabis was also comparatively slight (median 10 'intoxications' per lifetime), and tobacco usage was minimal (cigarettes/day: median = 0; inter-quartile 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.

Yet 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 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 did contain several tasks which were unimpaired, although some of these were simple measures which are not typically affected by MDMA (e.g. trail making A, ref: 13). The absence of deficits in tasks such trail making B, and California Word Learning, was however more surprising, since these sort of frontal executive task, and verbal memory task, are often impaired (13-20).

Halpern et al (1) divided their sample into two subgroups, with moderate users defined as less than 50 lifetime 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 however note that their heavier user subgroup did not

contain many heavy users – since only 6 of the 22 members of the heavy subgroup had taken MDMA on +150 occasions. The lifetime 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 as dose-related, with heavy users being relatively more impaired ($p = 0.003$ vs. 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 USA, 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, serotonin transporter (SERT) binding was significantly reduced in every region of the cerebral cortex (reductions ranging from -19% to -46%), and hippocampus (-21%). These SERT reductions were statistically associated with cumulative lifetime 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 Mc Cann et al (10), who had earlier reported significant correlations between reduced SERT binding and neurocognitive deficits. In an 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 lifetime 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 MDMA – ecstasy – serotonin – neurotoxicity - cognition – memory – executive function.

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