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REPLY

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The reality of psychomotor problems, and the possibility of Parkinson's disorder, in some recreational ecstasy/MDMA users: a rejoinder to Sumnall et al. (2003)

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Sumnall et al. (2003) raised several issues about our recent letter in Psychopharmacology (Parrott et al. 2003), and we welcome this opportunity to reply. Our letter was a commentary on the findings of Ricaurte et al. (2002) of dopaminergic damage in non-human primates, following an intensive dosing regimen with MDMA. It was written to address Ricaurte's question of why there was little evidence for Parkinson's disorder in regular ecstasy/MDMA users. So when Sumnall et al. (2003) noted the general paucity of reports describing Parkinson's disorder in ecstasy users, we can only agree with them, as would Ricaurte. The rationale for our letter was to note that there was preliminary evidence for a range of *other* psychomotor problems in some recreational ecstasy/MDMA users and to urge future investigations to be focused more broadly. We cited several lines of evidence, including subjective reports from our own studies (Parrott and Lasky 1998; Rodgers 2000). These two investigations were criticised by Sumnall et al. (2003) for not having polydrug user control groups. In fact both studies did include non-user controls, many of whom had taken other illicit drugs. Rodgers (2000) employed two control groups; one was of non-drug users and the other comprised cannabis users, some of whom had also used stimulants and hallucinogens in the past. Parrott and Lasky (1998) prospectively compared two ecstasy user groups with a non-user control group at a Saturday night dance, when the self-reported use of cocaine, amphetamine and cannabis was similar for all three groups. In both studies, the subjective complaints of psychomotor problems only emerged from a few of the ecstasy users, and, in every case, the problems were attributed to past MDMA use (see Parrott et al. 2003, for a summary of their experiences).

Sumnall et al. (2003) suggested that other ecstasy/MDMA studies have not reported significant psychomotor problems. They cited Cohen (1995), a large questionnaire survey of 500 MDMA users undertaken in 1992–1993. In that study, which incidentally did not have a control group, the majority of participants had a lifetime history of three ecstasy experiences or less. Yet, despite this, several 'long term recurring psychological and physical effects attributed to MDMA use' were reported (Table 2 in Cohen, 1995), including lower back pain (48%), neck hypertonicity (48%), depression (38%), and joint stiffness (36%), but psychomotor functioning was not otherwise assessed. However, another large questionnaire survey that covered various psychomotor functions was conducted by Topp et al. (1999). They assessed 329 heavy ecstasy/MDMA users and found a wide range of problems 'only related to ecstasy', including muscular aches (37%), numbness and tingling (59%), tremors and shakes (46%), along with many other physical and psychological problems. Most were acute or sub-chronic experiences, although a minority were off-drug (Tables 2 and 3 in Topp et al. 1999). Thus, motor problems do emerge when they are specifically addressed. Sumnall et al. (2003) also questioned whether these psychomotor/dopaminergic problems were dose related. Topp et al. (1999) generated an overall physical problem index, and

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found it to be significantly related to both the quantity of ecstasy normally used and to recent bingeing. We also confirmed the importance of dosage in our Internet-based study, where self-rated tremors/twitches attributed to ecstasy/MDMA were significantly related to the extent of past ecstasy/MDMA use, being reported by 14% of light users, 20% of moderate users and 38% of heavy users (Parrott et al. 2002).

The Sumnall group also noted the lack of evidence for dopaminergic neurotoxicity in humans. Here, we largely agree with them, but would like to note the findings from McCann et al. (1994), a laboratory comparison of 30 MDMA users and 28 controls, which has not been cited so far (Ricaurte et al. 2002; Parrott et al. 2003; Sumnall et al. 2003). They found significantly reduced serotonergic markers in both males and females, together with a reduction in dopaminergic indices which was statistically significant for females but not males. McCann et al. (1994, p 135) concluded: 'It is of note that MDMA-exposed women, in addition to having reduced cerebrospinal fluid 5-hydroxyindoleacetic acid, also have reduced cerebrospinal fluid homovanillic acid, a finding that is in keeping with the observation that at high dosage, MDMA can damage dopaminergic as well as serotonergic neurones (Commins et al. 1987)'. The empirical demonstration of striatal damage following MDMA in mice may also be pertinent. Ferrucci et al. (2002, p 75) noted: 'Movement disorders involve a number of degenerative conditions, mostly affecting basal ganglia.... We have found that 3,4-methyelendioxymethamphetamine (MDMA) produces ultrastructural alterations in striatal cells.... These morphological alterations were enhanced in locus coeruleus lesioned mice'. But the core question here is the paucity of evidence for dopaminergic loss in humans. In this regard, it should be noted that, if these motor problems are only occurring in a minority of users, then any overall group comparisons may well remain non-significant. Ricaurte et al. (2003) have also suggested that dopaminergic damage may only occur in MDMA bingers. Future studies could also focus on those who actively complain of psychomotor problems.

Sumnall and colleagues also noted that there should be an independent verification of symptoms. Again, we can only agree; indeed, that was implicit in our call for further research. Another important topic we both raised is the potential contribution of other psychoactive drugs in these extensive polydrug users (Scholey et al. 2003), especially dopaminergic stimulants such as amphetamine. Topp et al. (1999) found that stimulant use was not a predictive variable for their composite physical side-effect index (although stimulant bingeing was a predictor for psychological side effects). We also undertook a re-analysis of our www Internet data in order to address this question. Of the 87 individuals who had taken ecstasy at least once but never used amphetamine, 16 (18%) reported tremors and twitches that they attributed to ecstasy use. With the 195 people who had taken ecstasy and amphetamine at least once, 41 (21%) reported tremors and twitches that they attributed to ecstasy. These frequencies did not differ significantly (Chi-square=0.26; df=1, n=282), confirming the importance of ecstasy/MDMA rather than amphetamine. Nevertheless, future studies should continue to investigate the potential contributory role of all dopaminergic stimulants.

Sumnall also criticised the high and closed spaced doses employed by Ricaurte et al. (2002), noting that: 'Clearly, the dose regimen employed in this study was not analogous to common patterns of ecstasy use'. Yet the title of Ricaurte's article was: 'Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("Ecstasy")'. So who was correct ? Many recreational Ecstasy users certainly follow an intensive self-dosing regimen. Winstock et al. (2001) surveyed 1151 ecstasy-using clubbers, and found that over half (n=595) had taken five or more ecstasy/MDMA tablets on a single occasion, while 16% (n=171) had taken ten or more tablets in one session. An initial priming dose is typically followed by further tablets at spaced intervals; thus, Ricaurte was correct in noting the recreational use of closely spaced doses (Ricaurte et al. 2002, 2003). So why did Ricaurte's primates find this intensive dosing regimen so difficult to tolerate? The answer is almost certainly chronic tolerance (Parrott 2002, 2003). Novice ecstasy users typically only take a single tablet on their very first occasion (Hansen et al. 2001), but describe reduced subjective efficacy and dosage escalation with repeated usage (Parrott 2002). Chronic pharmacodynamic tolerance and increased self-dosing are thus characteristic of many regular users, and this probably reflects serotonergic neuronal loss or damage (Parrott 2003). This allows some experienced users to tolerate extremely high amounts of MDMA, such as 4 g pure MDMA over 24 h (Jansen 1999). Ricaurte et al. (2002) therefore used a dosing regimen appropriate for chronically tolerant recreational users, but which was probably excessive for naive laboratory animals with an unimpaired serotonin system.

The importance of Ricaurte's study for us, was the focus it gave to potential dopaminergic disorders in humans (Parrott et al. 2003). Psychomotor distress is certainly an area of concern for some ecstasy/MDMA users. In an Internet search undertaken this week, using 'twitch' and 'shakes' as keywords on the alt.drugs.ecstasy discussion group, the following personal accounts emerged: 'I now have twitches and a stutter in my voice sometimes.... never had the twitch or the stutter b4 I'm shitting it'; ... 'I know someone else who experiences uncontrollable twitching of the left eye which he claims he only got after he began doing E'; ... 'She also then started getting the shakes and convulsing every 10–15 seconds. she would just jerk her feet or clench her hands... this lasted about 2 hours'; ... 'She now shakes so profoundly that it is difficult for her to drink a cup of coffee'. It is unclear whether these problems will abate following drug cessation or whether, sooner or later, they may develop into a Parkinsonian Disorder (Ricaurte et al. 2003). Peroutka et al. (1988), cited in our original letter, noted that dopaminergic damage could occur in the

absence of symptoms, while Ricaurte et al. (2002) noted that Parkinsonism generally became manifest only when 70–80% of brain dopamine was depleted. However, the fourth case above is certainly of great concern and, with some individuals, it may unfortunately be sooner rather than later. Soon after the publication of our original letter in Psychopharmacology, we were indeed alerted to a case of Parkinson's Disorder in a former heavy MDMA user. Dr. MacMahon e-mailed us: 'I am a physician who specialises in PD in Cornwall, England. Can you point me to any longer term studies that could suggest what the prognosis may be for a young person displaying PD features after considerable MDMA exposure? I have such a case, and it would be helpful in his management'. We welcome advice on how best to respond.

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