Neuropsychopharmacology (2004) 29, 1940–1941

www.neuropsychopharmacology.org

Letter to the Editor

MDMA and the Loss of Reinforcement in Fantegrossi *et al* (2004)

Andy C Parrott*[,1]

[1]*University of Wales Swansea, UK*

Neuropsychopharmacology (2004) **29,** 1940–1941. doi:10.1038/sj.npp.1300538

Sir

Fantegrossi *et al* (2004) generated some very interesting findings in their investigation of changes in MDMA self-administration in rhesus monkeys, but I would like to question some of the interpretations they have offered for their data. They reported that the reinforcing effects of racemic MDMA, and R(−)-MDMA, reduced over time in rhesus monkeys, while S(+)-MDMA was 'more resistant to this effect'. However, while a general downshift emerged in the average dose–effect data from all three monkeys, it was less apparent in the individual monkey profiles. Instead, these demonstrated a mixture of rightward shifts, leftward shifts, downshifts, and even a few upward shifts (Figures 1–3). For instance with racemic MDMA, monkey 93X3577 reduced its responding to the low-dose condition, but maintained its initial rate of responding to the mid and high doses (Figure 1). With R(−)-MDMA, two of the monkeys reduced their responding to the low- and mid-dose conditions, but maintained their original response rates to the high-dose condition (Figure 3). This rightward shift towards higher doses were acknowledged in the Results: 'The final dose–effect curves for monkeys 93X3577 and 96X2484 each display a rightward shift when compared with their initial dose–effects curves…'. Yet surprisingly it was not debated in the Discussion, despite showing some close parallels with the human literature. Many regular Ecstasy users report that they need to take higher doses to achieve the desired subjective effects, and show dosage escalation, due to the development of chronic pharmacodynamic tolerance (Parrott, 2003, 2004). In contrast to the first two monkeys, the third animal (RC95) demonstrated a leftward shift with both racemic and R-MDMA; it maintained its original rate of responding only to the low-dose condition, and reduced its responses to the two higher doses (Figures 1 and 3).

*Correspondence: Professor AC Parrott, University of Wales Swansea, UK, E-mail: a.c.parrott@swan.ac.uk
Received 26 April 2004; accepted 28 May 2004
Online publication: 9 July 2004 at http://www.acnp.org/citations/Npp070904041 99/default.pdf

In their earlier report on the *acute* effects of self-administered MDMA in this cohort of animals, Fantegrossi *et al* (2002, p. 359) noted that: 'No individual animal is well represented by the aggregate group data'. This is also true for these longer-term findings (Fantegrossi *et al*, 2004). In particular, the suggestion that racemic MDMA and R(−)-MDMA lose their reinforcing effects over a period of repeated use seems to be an artefact of combining the data from all three animals. When the individual profiles are considered separately, each animal maintains its original level of self-reinforcement to at least one of the dose levels, while losing it to the others (Fantegrossi *et al*, 2004; Figures 1 and 3). The rightward shift is easy to model neurochemically, since it shows that MDMA is losing its reinforcing properties at *lower* dose levels. The occasional downwards and upwards shifts could also be modeled, although the leftward shift is more difficult to understand. However, in order to fully comprehend these shifts and changes, one really needs to know which of them was statistically significant; but somewhat surprisingly, no significance levels were presented, either for the group data, or for the individual profiles. In the Methods, it was noted that the neurochemical data were analyzed by ANOVA, but no statistical analysis procedures were described for the self-administration data. Instead they were presented visually, and interpreted without the usual significance levels. Ideally, one would have liked to see probability statements for the within-dose changes, in each individual animal.

My second area of concern relates to the statement in the Abstract that: 'There were no measurable decreases in serotonin (5-HT), or 5-hydroxyindoleacetic acid (5-HIAA)…in any brain region studied'. Yet in the body of the text one reads: 'Although not significant, downward trends in 5-HT were present in several brain regions following long term MDMA administration: depletion of 40–50% were evident in frontal, parietal, and temporal cortex, while lesser depletions (approximately 25%) were apparent in occipital cortex, thalamus, and hypothalamus…' (none in the hippocampus). Furthermore, the tabulated values were from four animals (Figure 6), including two which did not complete the full study, one due to methodological reasons, and another which had to be

euthanized just before final completion due to 'chronic health problems' (note: this animal showed the unexpected leftward dose–response shift, see above). This left just two monkeys who completed the full paradigm. The conclusion that self-administrated MDMA does not lead to any measurable changes in neuronal markers does therefore seem to be rather premature on the evidence presented. Nevertheless, despite these reservations, I found Fantegrossi *et al* (2004) a most intriguing study, and look forward to their further papers.

REFERENCES

Fantegrossi WE, Ullrich T, Rice KC, Woods JH, Winger G (2002). 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. *Psychopharmacology* **161**: 356–364.

Fantegrossi WE, Woolverton WL, Kilbourn M, Sherman P, Yuan J, Hatzidimitriou G *et al* (2004). Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. *Neuropsychopharmacology* **29**: 1270–1281.

Parrott AC (2003). Chronic tolerance to recreational ecstasy or MDMA: a new underlying mechanism? *J Psychopharmacol* **17**: a34.

Parrott AC (2004). Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or ecstasy. *J Psychopharmacol* **18** (in press).