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Reply to Dr Parrott

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

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Sir

We thank Dr Parrott for his careful reading of our paper. He raises several questions regarding the methodology and interpretation of data from our previous study 'Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys.' We wrestled with many of these same issues during the preparation of this manuscript. Indeed, our original experimental intentions for these monkeys had nothing whatsoever to do with the presently discussed results (Fantegrossi *et al*, 2004), but as we began to observe apparent changes in the reinforcing effects of MDMA we decided to change our objectives, strap in, and attempt to characterize the phenomenon as best we could.

In his letter, Dr Parrot noted that the 'before' and 'after' dose–effect curves for individual monkeys differ from the aggregate percent of control curves, and he is of course correct. Across a wide variety of pharmacological assays, it is often the case that the testing of more doses might shed light on changes in shapes, slopes, or intercepts of dose–effect curves. We would like to caution the reader that the patterns of changes observed in our MDMA self-administration dose–effect curves should not be characterized as 'leftward' shifts without the study of lower doses. A practical matter in generating dose–effect curves is that one must, at some point, choose to stop testing doses. In our study, we stopped when it was clear that the reinforcing effects of both racemic and R(−)-MDMA were changed. Specifically, at least one dose of each compound, that was initially self-administered at cocaine-like levels, engendered drastically reduced self-administration behavior following long-term exposure to MDMA. Importantly, this was true in every monkey tested. We therefore take exception to Dr Parrott's suggestion that the observed changes in reinforcing effects of MDMA are simply 'an artifact of combining the data from all three animals.' Results with S(+)-MDMA were less clear; we acknowledged this in the paper and believe it to be a potentially interesting area for future research.

With regard to statistical testing, we often forego this sort of analysis when using an n of 4 or less. In the case of the presently discussed experiments, we were simply too underpowered to generate a positive result. Indeed, this is why we insisted on presenting dose–effect curves for individual monkeys, although we are not aware of any widely accepted means to apply statistical analyses to within-subjects dose–effect curves.

During the writing of this report, we spent a fair amount of time discussing our serotonin (5-HT) findings among ourselves. As indicated in the manuscript, and as noted by Dr Parrott, nonsignificant trends toward 5-HT depletion were observed in several brain regions, although we saw no evidence whatsoever of 5-HT depletion in the hippocampus. This latter fact is quite notable as at least seven previous studies have detected >50% depletion in this brain region following noncontingent MDMA administration in Old World macaques (see our paper for further discussion). Our relatively small n limited the statistical power needed to detect significant changes in 5-HT in these studies, if they occurred. Whether increasing the number of subjects studied in these sorts of experiments would allow these nonsignificant trends to attain significance, or perhaps disappear via regression to the mean, is an empirical question that we are quite interested in answering through further study.

Again, we thank Dr Parrott for his careful reading of our report and for the opportunity to continue thinking about these provocative data.

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