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Reply to Nordstrom and Hart

Up in Smoke: Comparability of THC Dosing across Performance Studies

Johannes G Ramaekers*[,1], Gerold Kauert[2], Eef L Theunissen[1] and Manfred R Moeller[3]

[1]Experimental Psychopharmacology Unit, Faculty of Psychology, Maastricht University, Maastricht, The Netherlands; [2]Department of Forensic Toxicology, Institute of Legal Medicine, Goethe University of Frankfurt, Frankfurt, Germany; [3]Unikliniken des Saarlandes, Homburg, Germany

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Sir

We thank Drs Nordstrom and Hart (2006) for their comments, because it gives an opportunity to address an issue of growing importance in experimental cannabis research: the comparability of THC dosing across experimental performance studies. In general, researchers have employed two types of units for reporting the mean amount of THC delivered to subjects when smoking an experimental cannabis cigarette: (1) %THC contained in a cannabis cigarette and (2) absolute mass of THC (mg). The former provides only a relative measure of mass THC that cannot be used for comparison between studies that usually employ different sizes/weights of cannabis cigarettes. The latter provides an absolute measure of total amount of THC contained in a cigarette and is much to be preferred over relative units, because it does allow comparison of THC dose across studies. However, even comparison between absolute units of THC doses can be misleading because of variations in smoking procedures that are being employed across studies. It has been amply shown that variations in puff volume, number of puffs, and breathhold duration produce dose-related changes in plasma levels of THC (Azorlosa *et al*, 1995). Therefore, the best approach for increasing comparability between studies is to report THC dose as well as plasma THC concentrations. Unfortunately, assessment of plasma THC concentration is not standard practice in experimental performance research. However, if it were, it would have helped to evaluate the claims by Drs Nordstrom and Hart that THC doses in the studies by Hart *et al* (2001) and Ramaekers *et al* (2006) were comparable and that experienced cannabis users are tolerant to the impairing effects of THC on cognition. We will illustrate this point.

In their original publication, Hart *et al* (2001) did not indicate the total amount of THC that was delivered to their subjects by smoking. They merely indicated that their high concentration cigarettes contained 3.9% THC of which each subject smoked three standardized puffs. Each puff consisted of 5 s of inhalation, 10 s of breathhold, and 40 s of exhalation and rest. They failed to report the total mass of the cannabis cigarette. Nordstrom and Hart (2006) have now corrected this omission by stating that each cigarette weighed 1 g, on average of which subjects smoked three-quarters, within a 3 min period. This, they argue, is approximately 30 mg of THC which is close to the largest dose (35 mg) in the study by Ramaekers *et al* (2006). It is difficult to see, however, how subjects in the study by Hart *et al* (2001) could have smoked three-quarters of a cigarette in only three standardized puffs, when subjects in the study by Ramaekers *et al* (2006) needed about 25 standardized puffs, that is, 4 s of inhalation, 10 s of breathhold, and 15 s of exhalation and rest, to finish smoking a cannabis cigarette completely. These comparative data on THC dosing regimens certainly do not support the claim by Drs Nordstrom and Hart that the total amount of THC delivered to subjects were comparable in both studies. Of course, the final confirmation of their claim can only come from comparative plasma THC data. These however are not available, as Hart *et al* (2001) did not assess plasma THC. In addition, their claim is at odds with a previous conclusion by Hart *et al* (2002) that the behavioral effects of smoked cannabis containing 3.1% THC is similar to the effects of 20 mg oral THC. Again, no plasma THC data were provided but it is well established that bioavailability of oral THC is only 10% and generally three times lower as compared to smoked THC (McGilveray, 2005; Ohlsson *et al*, 1980). This seems to indicate that THC concentrations during the smoked condition in this and perhaps other experiments may have been very low as well. Of course, this is very speculative but it goes to show how data on plasma THC concentrations would have come in very handy.

*Correspondence: Dr JG Ramaekers, Experimental Psychopharmacology Unit, Faculty of Psychology, Brain and Behavior Institute, Maastricht University, PO Box 616, Maastricht 6200 MD, The Netherlands, Tel: +31 43 3881951, Fax: +31 43 3884125,
E-mail: j.ramaekers@psychology.unimaas.nl
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The second claim by Drs Nordstrom and Hart is that presence or absence of cognitive impairment during acute cannabis intoxication depends on cannabis use history. Thus, cognitive impairment is likely to occur in novice users as employed in the study by Ramaekers *et al* (2006) and unlikely to occur in frequent users as employed in the study by Hart *et al* (2001) owing to tolerance. There is much to be said for this claim in general, because tolerance to performance impairment has been shown for many drugs. Yet again, this claim cannot be evaluated very effectively in this particular case because Hart *et al* (2001) did not collect plasma THC data that is needed to exclude alternative explanations, or parts of them. Hart *et al* (2001) included daily cannabis users who all tested positive for THC in urine before smoking their experimental cannabis or cannabis placebo cigarette. Thus, the experimental placebo condition was actually a period of abstinence for these individuals and a period in which residual, low levels of THC may still have been present in blood. Both factors have been shown to contribute to cognitive impairment in cannabis users (Pope *et al*, 2001). In other words, the finding that cognitive performance of frequent cannabis users was comparable during THC and placebo treatments could have also reflected a presence of cognitive impairment during both treatment conditions. Again, assessment of plasma THC concentration during both treatments would have helped to interpret these results.

All of the above is not to discredit the work by Dr Hart and co-workers. On the contrary, their work has been of high standard for many years and has helped to significantly advance knowledge in the field. The main aim of the present response is to stress the importance of reporting THC dose as well as plasma THC concentrations in experimental performance studies.

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