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Correspondence

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Tryptophan depletion in addictive behaviours

We read with interest the article by Cox *et al*[1] and the insightful editorial by Nutt[2] and applaud both the research staff and the patients involved in this important study in view of the ethical issues and challenges in their work. They provide supportive evidence that low serotonin activity can increase dopaminergic responses to cocaine in humans, suggesting a possible mechanism specific to 'a low-serotonin state' in causing addictive behaviours. Although illuminating, the results of the study should be interpreted with caution.

First, Cox *et al* use acute tryptophan depletion producing a reduction in plasma tryptophan, assumed to represent low levels of serotonin in the brain. The primary neuropharmacological effect of cocaine is to block the uptake of monoamines released into synapses, thereby increasing synaptic monoamine availability. It has been shown that cocaine can increase extracellular levels of serotonin in the nucleus accumbens of rats.[3] Notably, in Cox *et al*'s study, plasma concentrations of tryptophan did not significantly differ between cocaine and placebo, which appears to be an unexpected finding. This should be left open to discussion. Second, the interplay between serotonin and cocaine may be altered after repeated cocaine administration,[4] a common manifestation in 'real-world' cocaine users. In this context, a study using an acute tryptophan depletion method plus repeated cocaine administration for patients with or without cocaine dependence, although ethically challenging, may obviously be of great clinical significance. Third, using repeated measures ANOVAs, it was assumed that the effects of cocaine did not carry over across conditions. Thus, it would have been clearer if the intervals between each condition were defined.

In addition to the issues raised by Nutt,[2] as to the differences in response to various drugs of addiction, we would like to suggest that future research in the field of addiction focuses on using the tryptophan depletion test. For example, we now know that in pathological gamblers, dopamine release in ventral striatum correlates with excitement levels during the Iowa Gambling Task.[5] However, tryptophan depletion significantly decreased, rather than increased, the number of decisions made to chase losses and the number of consecutive decisions to chase, independent of changes in mood.[6] These findings, indubitably, did not support the hypothesis that low serotonin transmission may predispose to increased susceptibility to impulsive behaviours. It would be of interest to investigate the extent to which tryptophan depletion regulates dopamine release in patients who gamble, or in other populations with addictive behaviours, such as internet addiction or sex addiction, under control of the relevant stimuli.

Finally, in the editorial by Nutt,[2] it is unclear as to the statement 'It seems that this might be the case as in Cox *et al*'s study lowering 5-HT function by tryptophan depletion led to a reduction in the actions of cocaine to release dopamine that was to some extent paralleled by a reduction in cocaine craving.' The study by Cox *et al* showed that low serotonin activity augmented, rather than diminished, dopamine release in response to cocaine.

In summary, Cox *et al*'s study[1] is a valuable contribution to the field of addiction, and we anticipate further studies examining the relationship between experimental reductions in serotonin activity and endogenous dopamine release in various addictive behaviours under control of the relevant stimuli.

1 Cox SML, Benkelfat C, Dagher A, Delaney JS, Durand F, Kolivakis T, et al. Effects of lowered serotonin transmission on cocaine-induced striatal dopamine response: PET [^{11}C]raclopride study in humans. *Br J Psychiatry* 2011; **199**: 391–7.

2 Nutt D. Low serotonergic tone and elevated risk for substance misuse. *Br J Psychiatry* 2011; **199**: 353–4.

3 Teneud LM, Baptista T, Murzi E, Hoebel BG, Hernandez L. Systemic and local cocaine increase extracellular serotonin in the nucleus accumbens. *Pharmacol Biochem Behav* 1996; **53**: 747–52.

4 Filip M, Bubar MJ, Cunningham KA. Contribution of serotonin (5-hydroxytryptamine; 5-HT) 5-HT$_2$ receptor subtypes to the hyperlocomotor effects of cocaine: acute and chronic pharmacological analyses. *J Pharmacol Exp Ther* 2004; **310**: 1246–54.

5 Linnet J, Moller A, Peterson E, Gjedde A, Doudet D. Dopamine release in ventral striatum during Iowa Gambling Task performance is associated with increased excitement levels in pathological gambling. *Addiction* 2011; **106**: 383–90.

6 Campbell-Meiklejohn D, Wakeley J, Herbert V, Cook J, Scollo P, Ray MK, et al. Serotonin and dopamine play complementary roles in gambling to recover losses. *Neuropsychopharmacol* 2011; **36**: 402–10.

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Authors' reply: Liang & Ho raise a number of interesting points. First, participants were tested following cocaine ingestion while in a low serotonin *v.* control state. Investigating the effects of repeated cocaine use in these states, we agree, would be interesting. Second, cocaine ingestion did not alter plasma tryptophan levels. We consider this a strength. Although acute cocaine administration increases extracellular serotonin levels, this need not be associated with decreased tryptophan levels in the periphery. In comparison, tryptophan levels fell as expected after the acute tryptophan depletion procedure, changes that are indicative of decreased availability of the serotonin precursor in brain. Third, Liang & Ho cite recent work indicating that greater striatal dopamine release in pathological gamblers correlates with higher subjective excitement and poorer performance during the Iowa Gambling Task.[1,2] Our own study raises the possibility that individuals exhibiting the largest dopamine responses might have lower serotonergic tone. Although Campbell-Meiklejohn *et al*'s elegant study[3] suggests that low serotonin increases sensitivity to punishment when healthy participants perform an unfamiliar task, other work indicates that serotonin induces the opposite effect in response to highly salient rewards.[4] Moreover, numerous impulsivity subcomponents have been proposed, and serotonin's contribution to them seems to vary. Fourth, the minimum time between cocaine test sessions was 2 days, well beyond the drug's plasma half-life of 40–60 min. Average time between test sessions 1 and 2 was 30 days (s.d. = 19), and 36 days (s.d. = 46)

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