

Invited Letter Rejoinder

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Reply to Vadhan *et al.* – Correspondence on Curran *et al.* (2018) ‘Which biological and self-report measures of cannabis use predict cannabis dependency and acute psychotic-like response’


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We thank our esteemed colleagues at Colombia University for their interest in our recent publication in this journal (Curran *et al.*, 2018).

In our paper we aimed to investigate the relationship between a wide range of biological and self-report measures of cannabis use and two key outcomes: cannabis dependence and acute psychotic-like response to the drug. We included an unprecedented set of 15 different cannabis use measures taken from participants’ hair, urine, their own cannabis samples, and self-report to estimate exposure to delta-9-tetrahydrocannabinol (THC) and cannabidiol. We found that a combination of urinary and self-report measures was associated with both of these outcomes. Cannabis dependency was predicted by higher frequency of cannabis use and urinary THC-COOH/creatinine concentrations. Acute psychotic response to cannabis was predicted by a higher age of first use and lower urinary THC-COOH/creatinine concentrations, suggestive of tolerance to this acute effect.

In contrast, the letter by Vadhan *et al.* raises a separate question of whether psychosis proneness predicts the acute psychotic response to cannabis. Although this question is beyond the scope of our recent paper, we agree it is an important question. Indeed we have addressed this issue in previous publications. The first of these showed that a measure of psychosis-proneness (the Schizotypal Personality Questionnaire – SPQ, Raine, 1991) predicted the acute psychotic response to cannabis (Mason *et al.*, 2009). The acute psychotic response was measured with the Psychotomimetic State Inventory (PSI), the same measure we used in Curran *et al.* (2018). In a second study, we showed that variation at the rs2494732 locus of the AKT1 gene predicts the acute psychotic response to cannabis on the PSI. This parallels studies with people diagnosed with a psychotic disorder where the AKT1 rs2494732 polymorphism also interacts with cannabis to predict the risk of psychosis (van Winkel *et al.*, 2008, 2011; di Forti *et al.*, 2012). Our previous paper (Morgan *et al.*, 2016) was focused on psychosis proneness, and did not include the same comprehensive set of 15 biological and subjective measure of cannabis use as Curran *et al.* (2018). However, it did include years of cannabis use and cannabis dependency as possible predictors. Using a multiple regression model we found that increased dosage of the C allele on the AKT1 rs2494732 genotype, increased baseline psychotic symptoms, and fewer years of cannabis use predicted acute psychotic symptoms following cannabis use. We hope that these analyses in our previous paper (Morgan *et al.*, 2016) sufficiently address the points raised by Vadhan *et al.*

In conclusion, we agree with Vadhan *et al.* that psychosis proneness is an important factor to consider when investigating the acute psychotic response to cannabis, as we have shown in our previous work (Mason *et al.*, 2009; Morgan *et al.*, 2016). As the field progresses it will be important to investigate other predictors of vulnerability and resilience such as adolescent onset of use (Mokrysz *et al.*, 2016) and comprehensive assessments of cannabis use (Curran *et al.*, 2018). Indeed, measures of cannabis use are typically poor in research studies at present, and require standardisation to improve precision when measuring cannabis use and its association with harms and benefits of use (Lorenzetti *et al.*, 2016; Hindocha *et al.*, 2017).

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