After decades of opposition, a resurgence of interest in the psychotherapeutic potential of LSD is gaining acceptance in the medical community. Future acceptance of LSD as a psychotherapeutic adjuvant may be predicated on knowledge about its neural mechanisms of action. Preclinical drug discrimination assay offers an invaluable model to determine the neural mechanisms underlying LSD's interoceptive stimulus effects. Unfortunately, current preclinical literature on LSD discrimination is based on results obtained exclusively in male subjects. The present study represents the first known preclinical assessment of possible sex differences in the discriminative stimulus effects of LSD.
Adult female (n=8) and male (n=8) Sprague-Dawley rats were trained to discriminate 0.08 mg/kg LSD from saline under a fixed ratio 20 schedule of food reinforcement. Once discrimination was established, substitution tests were conducted with other hallucinogens (mescaline, DOM, psilocybin), mixed psychedelic-stimulants (MDMA, (+)-MDMA, (-)-MDMA, (+)-MDA, (-)-MDA), synthetic cathinones (MDPV, mephedrone) and psychostimulants (cocaine, amphetamine). Antagonist tests were conducted with serotoninergic antagonists (WAY 100,635, MDL 100,907, pirenperone) and dopaminergic antagonists (haloperidol, SCH 23390).

Stimulus substitution results indicate higher levels of LSD-substitution with other serotonergic hallucinogens in females compared to males and some evidence for sex differences in the level of partial substitution by synthetic cathinones and the enantiomers of MDMA and MDA. Specifically, greater partial substitution was observed with (±)-MDMA, (+)MDMA, and (+)-MDA, in males and greater partial substitution was observed with (-)-MDMA, (-)-MDA, MDPV, and 4-MMC in females. Dopamine antagonists failed to block LSD in either males or females, but had stronger rate suppressant effects in males. The 5-HT2A antagonist, MDL 100,907 blocked LSD discrimination in both males and females, although complete blockade was evident at lower doses in males. These results suggest the relative contribution of serotonergic versus dopaminergic activity to the LSD cue varies between males and females. These findings may be informative for future investigations with human populations regarding possible sex differences in the subjective effects of LSD.