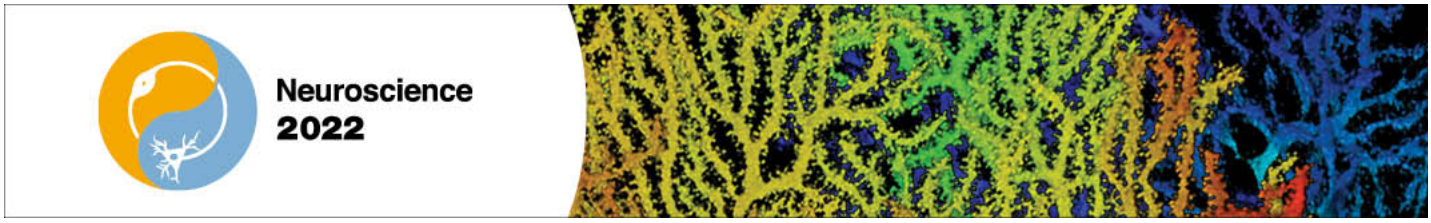

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Effects of oral Lactobacillus spp. pretreatment on sensitized response induced by repeated smoked cocaine and the influence on gut microbiota structure

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Abstract:
Emerging studies highlight the potential role of intestinal microbiota (IM) modulation in brain disorders; however, studies addressing its involvement in substance use disorder (SUD) are limited. Cocaine systemic administration in rodents induces gut dysbiosis and chronic antibiotics enhance its rewarding property. Accordingly, we demonstrated that repeated exposure to volatilized cocaine (14 days) alters the IM structure and diversity in rats, leading to hypothesized that IM modulation by probiotic bacteria can attenuate cocaine effects. The present study aims to evaluate the role of the IM modulation on the changes induced by the chronic administration of smokable cocaine on locomotor sensitization, and IM structure. Adult male Wistar rats were administered via oral syringe-feeding with a bacterial mixture of three probiotic Lactobacillus strains (*L. johnsonii* ATCC 33200; *L. rhamnosus* GG ATCC 53103; *L. reuteri* ATCC 23272; 1x10E8 CFU in 0.5 ml) or vehicle (skim milk) for 28 days. From day 22 to 28, rats were also daily exposed to cocaine (7 days/25 mg) by pulmonary inhalation, and locomotor activity in the open field was assessed. Fecal samples were collected at different time points and processed for DNA extraction, sequencing and posterior microbiota analysis. Behavioral results showed that oral bacteria administration did not *per se* affect locomotor activity. In cocaine-exposed rats we observed a progressive stimulant effect (locomotor sensitization) from day 1 to 5 of cocaine, and decreased in days 6 and 7. Bacteria administration did not prevent cocaine sensitization, and maintained the motor activity elevated until the last day. On day 28, no significant differences were found in the microbiota structure in cocaine-exposed animals in comparison with the control group. However, animals administered with bacteria and exposed to cocaine showed differences in their IM structure compared to bacteria control group ($p=0.038$), and tend to differ concerning the cocaine group ($p=0.052$). All these results suggest that 7 days of volatilized cocaine are not enough to significantly change IM structure, but an influence of bacterial mixture pretreatment was observed, suggesting a possible role in the sustained cocaine-stimulant effect. Altogether our findings provide information about the role of gut-brain axis in SUD. Further experiments should be done to evaluate the potential benefits of other bacterial strains for microbial-based therapeutic strategy in SUD.

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