The serotonergic hallucinogen 5-Methoxy-N,N-dimethyltriptamine (5-MeO-DMT) disrupts cortical function. Reversal by antipsychotic drugs.

INTRODUCTION
5-MeO-DMT (component of Ayahuasca, an Amazonian beverage) is a natural indoleamine hallucinogen with non-selective serotonin 5-HT₂A/5-HT₃A receptor agonist properties. Its ability to cause physiological and behavioural changes such as hallucinations can be used to study the neurobiological basis of psychotic symptoms in schizophrenia. We previously reported that 5-MeO-DMT (component of Ayahuasca) disrupts cortical function in rodents and the potential reversal of its action by antipsychotics.

AIMS
To examine the effect of the hallucogenic 5-MeO-DMT on mPFC activity (Low frequency cortical oscillations-LFCO- and pyramidal discharge).

To examine the 5-HT receptors potentially involved (5-HT₁A and 5-HT₂A) in 5-MeO-DMT effects using selective antagonists and 5-HT₂A receptor knockout mouse (KO2A).

To examine the action of 5-MeO-DMT on monoamine release (DA and 5-HT) in mPFC in WT and KO2A mice in parallel to behavior changes.

To examine the potential reversal of 5-MeO-DMT by marketed antipsychotic drugs (Haloperidol, non-selective D₂-R antagonist; Risperidone non-selective 5-HT₂A antagonist) and the mGlu2/3 receptor agonist (LY379268).

The present study aims to examine brain areas involved using blood-oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) and the 5-HT receptors potentially involved (5-HT₁A and 5-HT₂A) in 5-MeO-DMT effects using selective antagonists and 5-HT₂A receptor knockout mice (KO2A).

To examine the potential reversal of 5-MeO-DMT by marketed antipsychotic drugs (Haloperidol, non-selective D₂-R antagonist; Risperidone non-selective 5-HT₂A antagonist) and the mGlu2/3 receptor agonist (LY379268).

The natural hallucinogen 5-MeO-DMT (0.1 mg/Kg i.v.), in combination with clorgyline, altered pyramidal discharge (increasing and decreasing by activity of 51% and 35% of the recorded neurons, respectively) and considerably reduced LFCO (to 64±2% of basal values) in rat mPFC.

5-MeO-DMT and the mGlu2/3 receptor agonist LY379268 in rat visual primary cortex in KO2A mice.

Local perfusion of 5-MeO-DMT alters mPFC 5-HT release in mPFC via 5-HT₁A-R in mice. The reduction in LFCO induced by 5-MeO-DMT in rat mPFC is reversed by WAY100635 (5-HT₁A receptor antagonist) and M100907 (0.3 mg/Kg); LY379268 (LY, 0.5-1.5 mg/Kg) reduce LFCO to 64±2% of basal values in mouse mPFC. Moreover the present results point to the prefrontal and sensorial cortical areas as sites of action of this hallucinogen and suggest the involvement of 5-HT₁A receptors in the action of indoleamine hallucinogens, in addition to their well-known action on 5-HT₂A receptors.

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CONCLUSIONS
Together with previous findings (1-3), the present results indicate that reductions in LFCO are a common neurophysiological signature of hallucinogens. The reversal of these effects by antipsychotic drugs with different mechanisms of action suggests a clear association with their therapeutic activity, regardless of their initial pharmacological target. This supports the usefulness of the LFCO model in PFC to examine the neurobiological basis of hallucinations and in target identification during antipsychotic drug development.

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REFERENCES
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Materials and Methods
Animals: Male adult Wistar rats (250-300 g) and male C57Bl/6 WT and KO2A mice (9-15 weeks).
Anesthesia: Chloral hydrate 450 mg/kg i.p. Pentobarbital Sodium: 40 mg/kg i.p. (Electrophysiology and MRI).

Methods:
Dialysate DA (% of basal values) and 5-HT (% of basal values) in S1, Au1 and V1 respectively.

Electrophysiological recordings: Single unit extracellular recording of pyramidal neurones in mPFC identified by antinomic admeasion from ventral tegmental area. Local field potential (LFP) in rPFC and Episodic Electrocoriocogram (EECoG) in S1, Au1 and V1.

Behaviour: Stereotypes associated to 5-HT₂A+5-HT₁A receptor activation (tremor and head twitch response –TMR, respectively).

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Authors declare no conflict of interest