

Differential effects of psilocybin and lisuride on serotonin and dopamine neuronal activity and behavior

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ABSTRACT

Psilocybin and lisuride are 5-HT_{2A} receptor agonists, but only psilocybin elicits the head twitch response (HTR) in rodents, a behavior commonly used as a proxy for hallucinogenic activity. This study aimed to compare their effects on serotonin (5-HT) and dopamine (DA) neuronal activity, as well as related behavioral outcomes, to elucidate the mechanisms underlying their divergent effects. Adult male C57BL/6N mice were administered intraperitoneal injections of psilocybin (0.3–3 mg/kg), lisuride (0.1–0.5 mg/kg), or vehicle. *In vivo* electrophysiological recordings were performed in the dorsal raphe nucleus (DRN) and substantia nigra (SN) to monitor 5-HT and DA neuronal firing. MDL 100907 (0.2 mg/kg) pretreatment was used to determine 5-HT_{2A} receptor specificity. Behavioral assessments included HTR testing 10 min post-injection, followed by either the forced swim test (FST), open field test (OFT), or elevated plus maze (EPM) at 20 min post-injection. Psilocybin-induced inhibition, but not lisuride-induced inhibition, of 5-HT neuron firing was blocked by MDL 100907. Both drugs reduced DA neuron firing, however, lisuride's effect was more sensitive to 5-HT_{2A} receptor antagonism. Psilocybin elicited HTR, while lisuride did not. In the FST, only high-dose lisuride reduced immobility time. Both drugs reduced locomotor activity in the OFT and EPM. Principal Component Analysis (PCA) sufficiently separated the effects of each drug from each other, indicating distinct effect profiles. Although both drugs target 5-HT_{2A} receptors, they engage distinct neurobiological pathways. Psilocybin produces psychedelic-like, 5-HT-dominant effects, whereas lisuride displays DA-linked improvements in coping behavior, informing future development of serotonergic therapeutics.

1. Introduction

Psychedelics represent potential novel therapies in psychiatry (Bogenschutz et al., 2022; Carhart-Harris et al., 2021), such as major depression (Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin et al., 2022; Goodwin et al., 2023). The serotonin type 2A (5-HT_{2A}) receptor mediates psychedelic effects in humans (Preller et al., 2017) and

its proxy, the head twitch response (HTR), in rodents (Halberstadt et al., 2020).

Recent observations raise the possibility that clinically relevant effects might be elicited by 5-HT_{2A} receptor agonism in the absence of psychedelic or dissociative effects (Cameron et al., 2021). For example, lisuride is structurally similar to lysergic acid diethylamide (LSD) and acts as a 5-HT_{2A} receptor agonist (Glatfelter et al., 2024). However,

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unlike classical psychedelics such as LSD or psilocybin, lisuride does not produce psychedelic effects in humans or trigger the HTR in rodents (de la Fuente Revenga et al., 2022; Glatfelter et al., 2024; Herrmann et al., 1977).

Psilocybin is a prodrug that is rapidly dephosphorylated to psilocin, which exhibits high affinity for several serotonergic receptors in mice, particularly 5-HT_{2A} (K_i = 110–173 nM), 5-HT_{1A} (K_i = 113–146 nM), and 5-HT_{2C} (K_i = 79–311 nM) (Erkizia-Santamaría et al., 2022; McGriff et al., 2025). Lisuride, a non-hallucinogenic ergoline, also binds with high affinity to serotonergic receptors, including 5-HT_{2A} (K_i = 4.9–16.6), 5-HT_{1A} (K_i = 1.5–3.1 nM), and 5-HT_{2C} (K_i = 18.9–21.1), but differs in its functional activity depending on the receptor subtype (Egan et al., 1998; Glatfelter et al., 2024). Importantly, lisuride also exhibits significant dopaminergic activity through D₂ receptor (K_i = 2.9–4.1 nM) (De Keyser et al., 1995). Through these receptors, lisuride and psychedelics impact serotonin and dopamine activity (De Gregorio et al., 2016; Fuxe and Calne, 1979; Gessa, 1988; Pulvirenti and Koob, 1992; Qu et al., 2023; Rogawski and Aghajanian, 1979).

Clinically, lisuride is already approved in several countries for the treatment of hyperkinetic movement disorders such as Parkinson's disease (Lieberman et al., 1981), and has been shown to have antidepressant properties in post-stroke depression patients (Hougaku et al., 1994; Parkes et al., 1981) and preclinical paradigms (Pogorelov et al., 2023; Qu et al., 2023). These unique properties make lisuride a valuable comparator compound for disentangling the hallucinogenic and therapeutic actions of 5-HT_{2A} receptor agonists. Understanding the mechanistic divergence between lisuride and psychedelic compounds like psilocybin may inform the development of next-generation serotonergic therapeutics that retain beneficial effects on mood and cognition while minimizing psychedelic liability.

The aim of this study was to compare the effects of psilocybin and lisuride on the spontaneous firing activity of serotonergic (5-HT) neurons in the dorsal raphe nucleus (DRN), a key source of serotonin projections to brain regions involved in mood regulation and antidepressant responses (Gobbi and Blier, 2005). Building on previous findings from our lab showing that LSD inhibits DRN firing at low doses via 5-HT_{2A} receptor activation (De Gregorio et al., 2022; De Gregorio et al., 2016), we tested whether psilocybin and lisuride exhibit similar 5-HT_{2A}-dependent inhibitory effects. In addition, we investigated their impact on dopaminergic (DA) neuron activity in the substantia nigra (SN), a region critically involved in motor control and involuntary movement regulation (Haber and Fudge, 1997). To further explore functional differences between the two compounds, we assessed behavioral outcomes including coping behavior in the forced swim test (FST), locomotor and anxiety-like responses in the open field test (OFT) and elevated plus maze (EPM), and burrowing behavior, an unconditioned measure of exploratory drive.

2. Material and methods

2.1. Animals

A total of 306 male C57BL/6N mice (8–12 weeks old, 25–35 g; Charles River, Quebec, Canada) were used in this study. All procedures were conducted in accordance with ethical guidelines to minimize animal suffering, and the principles of the 3Rs (Replacement, Reduction, and Refinement) were applied wherever possible. Accordingly, group sizes ranged from 5 to 21 animals for behavioral experiments and from 3 to 8 animals for electrophysiological recordings. The procedures were approved by the McGill University Ethics Committee and the McGill Comparative Medicine and Animal Resources Center (protocol #5764) and conducted in accordance with the Canadian Council on Animal Care Guidelines and the Canadian Institute of Health Research for Animal Care and Scientific Use.

2.2. In vivo extracellular electrophysiological testing

For the electrophysiological experiments, our standard laboratory approach was used (De Gregorio et al., 2022; De Gregorio et al., 2021; De Gregorio et al., 2016). This involved acute intraperitoneal (i.p.) injection of vehicle (97 % saline plus 3 % Dimethylsulfoxide [DMSO]) or MDL 100907 (0.2 mg/kg), then 10 min later mice received injections of psilocybin or lisuride every 300 s, resulting in cumulative doses of 0.5, 1, 2, and 3 mg/kg of psilocybin, or 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg of lisuride (Fig. 1A and 2A). The dose that produced maximal inhibition of 5-HT neuronal firing was selected as the highest dose in the behavioral dose–response experiments, to directly relate electrophysiological effects to behavioral outcomes. Previous work with LSD in our laboratory (De Gregorio et al., 2022; De Gregorio et al., 2021), along with findings from both electrophysiological and behavioral studies of selective serotonin reuptake inhibitors (SSRIs), support a link between reduced dorsal raphe nucleus (DRN) 5-HT neuronal activity and therapeutic effects (Hajós et al., 1995; Lucki et al., 1994).

2.3. Behavioral testing

Psilocybin (0.3, 1, or 3 mg/kg, i.p.), lisuride (0.05, 0.15, or 0.5 mg/kg, i.p.), or vehicle were administered. Immediately thereafter, mice were placed in a transparent polycarbonate cage (20 cm × 13 cm × 38 cm) to measure the number of HTR events for 10 min. Subsequently, mice were returned to their home cage for 10 min before having them undergo additional behavior tests (Fig. 3A). A full detailed description of the methods is presented in the supplementary material file.

3. Results

3.1. Psilocybin and lisuride inhibit DRN 5-HT firing activity, but only the psilocybin-induced inhibition is prevented by the 5-HT_{2A} receptor antagonist MDL 100907

We have previously demonstrated that LSD acutely inhibits DRN 5-HT firing activity, similar to several classes of antidepressants (De Gregorio et al., 2016; Gobbi and Blier, 2005). To further investigate other psychedelics and non-psychedelic analogues, and their effective doses, we measured the effects of psilocybin (0.5–3 mg/kg, i.p.) and lisuride (0.1–0.5 mg/kg, i.p.) on DRN 5-HT firing activity. First, we confirmed that increasing doses of psilocybin (0.5–3 mg/kg) decreased firing activity in 5 out of 5 DRN 5-HT neurons (one neuron per mouse). We then also confirmed the effects of increasing doses of lisuride (0.1–0.5 mg/kg) in 5 out of 5 DRN 5-HT neurons. Next, we tested whether the 5-HT inhibition was mediated by 5-HT_{2A} receptors, using the 5-HT_{2A} receptor antagonist MDL 100907 (0.2 mg/kg, i.p., 10 min before psilocybin or lisuride). Fig. 1B and E depict the effect of psilocybin and lisuride on DRN 5-HT neurons, respectively, following i.p. injection of cumulative doses.

Vehicle plus psilocybin (0.5–3 mg/kg) produced a dose-dependent decrease in DRN 5-HT firing frequency that was prevented by MDL 100907, (Two-way ANOVA for dose $F_{(2,551, 21.68)} = 10.45$, $p = 0.0003$; pre-treatment $F_{(1, 9)} = 15$, $p = 0.0035$; interaction $F_{(4, 34)} = 6.224$, $p = 0.0007$). The post-hoc analysis indicated that psilocybin significantly decreased DRN 5-HT activity, compared to the vehicle baseline, at the dose of 2 mg/kg ($p = 0.0002$) and 3 mg/kg ($p = 0.0052$; Fig. 1B). After MDL 100907 injection, none of the psilocybin doses tested significantly decreased DRN 5-HT firing activity. Moreover, when the curve vehicle plus psilocybin was compared to that of MDL 100907 plus psilocybin, we found significant differences at 1 mg/kg ($p = 0.0407$), 2 mg/kg ($p = 0.0038$), and 3 mg/kg ($p = 0.0080$; Fig. 1B). We then compared the percentage (%) of the area under the curve (AUC) between vehicle plus psilocybin and MDL 100907 plus psilocybin (see supplementary section 2.2 for calculation method) and found that the dose response was significantly greater for MDL 100907 plus psilocybin compared to that

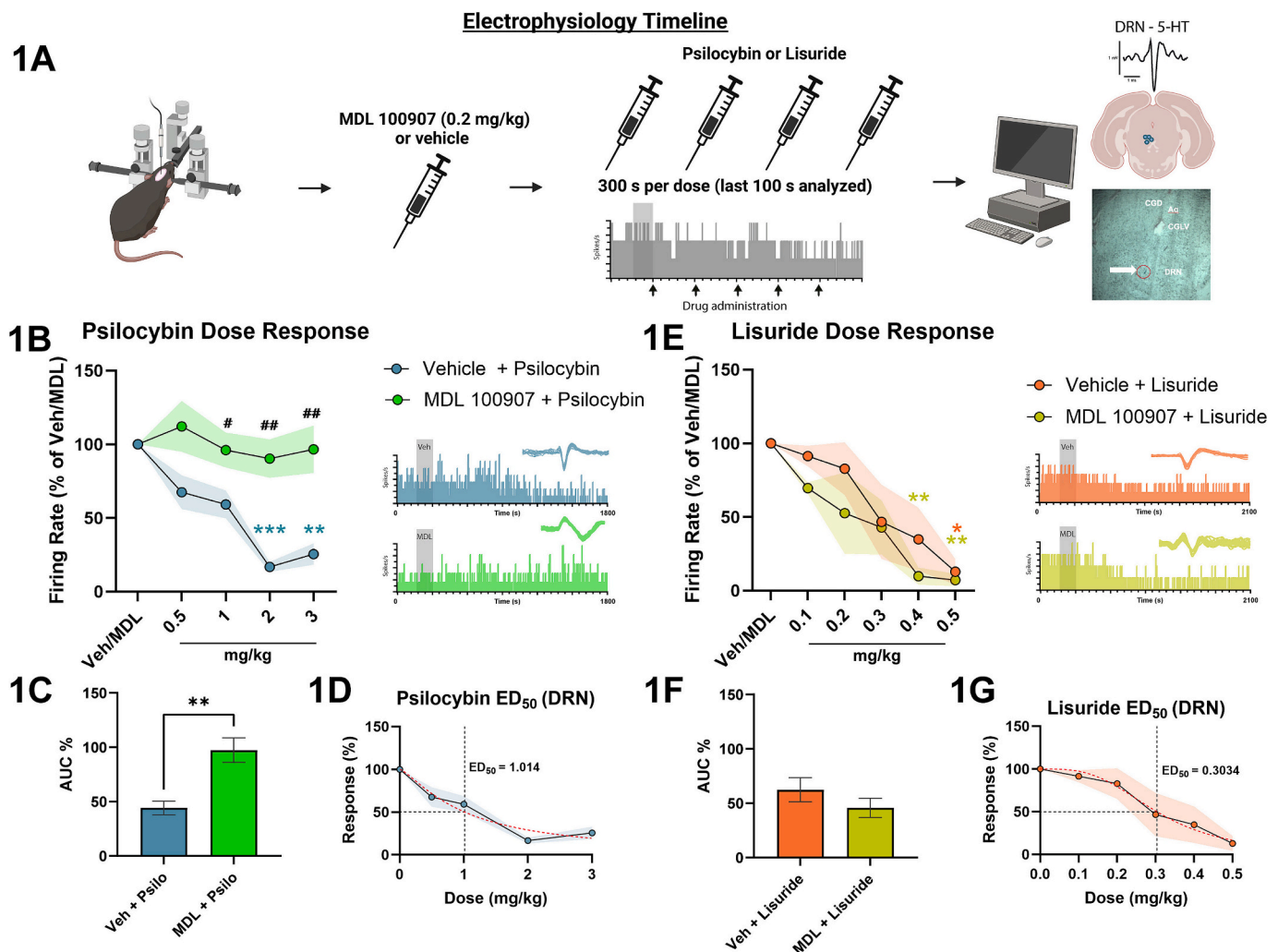


Fig. 1. Effects of psilocybin and lisuride on the firing activity of dorsal raphe nucleus (DRN) serotonin (5-HT) neurons. (1A) A schematic representation of the experimental timeline with the coronal section of the mouse brain, photomicrograph of the recording site in the DRN and the typical waveform. Each dose response is accompanied with representative integrated firing rate histograms showing the acute response of neurons to psilocybin (0.5, 1, 2, and 3 mg/kg, i.p.) and lisuride (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg, i.p.). Change in firing rate is calculated by percentage (%) changed from vehicle (Veh) or MDL 100907 (MDL; 0.2 mg/kg, i.p.) administration. (1B–1C) Psilocybin ($n = 6$) dose-dependently inhibits the firing rate of DRN 5-HT neurons, blocked by MDL 100907 ($n = 5$). (1C) A comparison of the percentage (%) area under the curve (AUC) between vehicle + psilocybin and MDL 100907 + psilocybin. (1D) non-linear regression analysis (variable slope - 4 parameter; $R^2 = 0.71$) of the psilocybin dose response to obtain the ED₅₀. (1E–1F) Lisuride ($n = 5$) at the highest dose (0.5 mg/kg, i.p.) inhibits the firing rate of DRN 5-HT neurons, and combined with MDL 100907 ($n = 4$) inhibits the firing rate of DRN 5-HT neurons at 0.4 and 0.5 mg/kg (i.p.). (1F) A comparison of the percentage (%) area under the curve (AUC) between vehicle + lisuride and MDL 100907 + lisuride. (1G) non-linear regression analysis (variable slope - 4 parameter; $R^2 = 0.98$) of the lisuride dose response to obtain the ED₅₀. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to vehicle (Veh) treated mice, # $p < 0.05$, ## $p < 0.01$ compared to mice of the same dose group between conditions (e.g., vehicle + psilocybin 0.5 mg/kg vs. MDL 100907 + psilocybin 0.5 mg/kg). DRN - dorsal raphe nucleus, 5-HT - serotonin, ED₅₀ - effective dose to cause 50 % of a response, AUC % - area under the curve percentage, Veh - vehicle, MDL - MDL 100907.

of vehicle plus psilocybin, $t_{(9)} = 4.268$, $p = 0.0010$ (Fig. 1C). The ED₅₀, calculated from the dose response curve following vehicle plus psilocybin injection (see supplementary section 2.2 for calculations) was 1.014 mg/kg (Fig. 1D).

We also found that vehicle plus lisuride (0.1–0.5 mg/kg) produced a dose-dependent decrease of DRN 5-HT firing frequency, which was not prevented by MDL 100907 (Two-way ANOVA for dose $F_{(2,256, 13.54)} = 17.14$, $p = 0.0001$; pre-treatment $F_{(1, 7)} = 1.43$, $p = 0.2707$; interaction $F_{(5,30)} = 0.4461$, $p = 0.8127$). Post-hoc analysis revealed that lisuride significantly decreased DRN 5-HT activity at the dose of 0.5 mg/kg ($p = 0.0326$). Similarly, MDL 100907 plus lisuride decreased DRN 5-HT activity with significant effects at the doses of 0.4 mg/kg ($p = 0.009$) and 0.5 mg/kg ($p = 0.003$; Fig. 1E), suggesting a potentiation by the 5-HT_{2A} receptor antagonism over lisuride, at least at the dose of 0.4 mg/kg. Moreover, the AUC % of the dose-response curve did not significantly differ between vehicle plus psilocybin and MDL 100907 plus psilocybin,

$t_{(7)} = 1.133$, $p = 0.1472$ (Fig. 1F). The ED₅₀ of lisuride's inhibitory effect was 0.3034 mg/kg (Fig. 1G).

Previous studies indicate that some 5-HT neurons (10–43 %) exhibit a bursting activity pattern (De Gregorio et al., 2022; Hajós and Sharp, 1996). We found that of 6 out of 11 DRN 5-HT neurons treated with vehicle plus psilocybin, and 8 out of 9 treated with MDL 100907 plus psilocybin exhibited bursting activity, without significant difference between the two groups ($p = 0.06$). Reports of the raw burst data and analysis for DRN 5-HT neurons, and changes induced by psilocybin or lisuride, can be found in the supplementary file (supplementary section 4: Table 1–2).

3.2. Psilocybin and lisuride inhibit SN DA firing activity, but only lisuride inhibition is prevented by the 5-HT_{2A} receptor antagonist MDL 100907

We then investigated if psilocybin and lisuride also inhibited SN DA

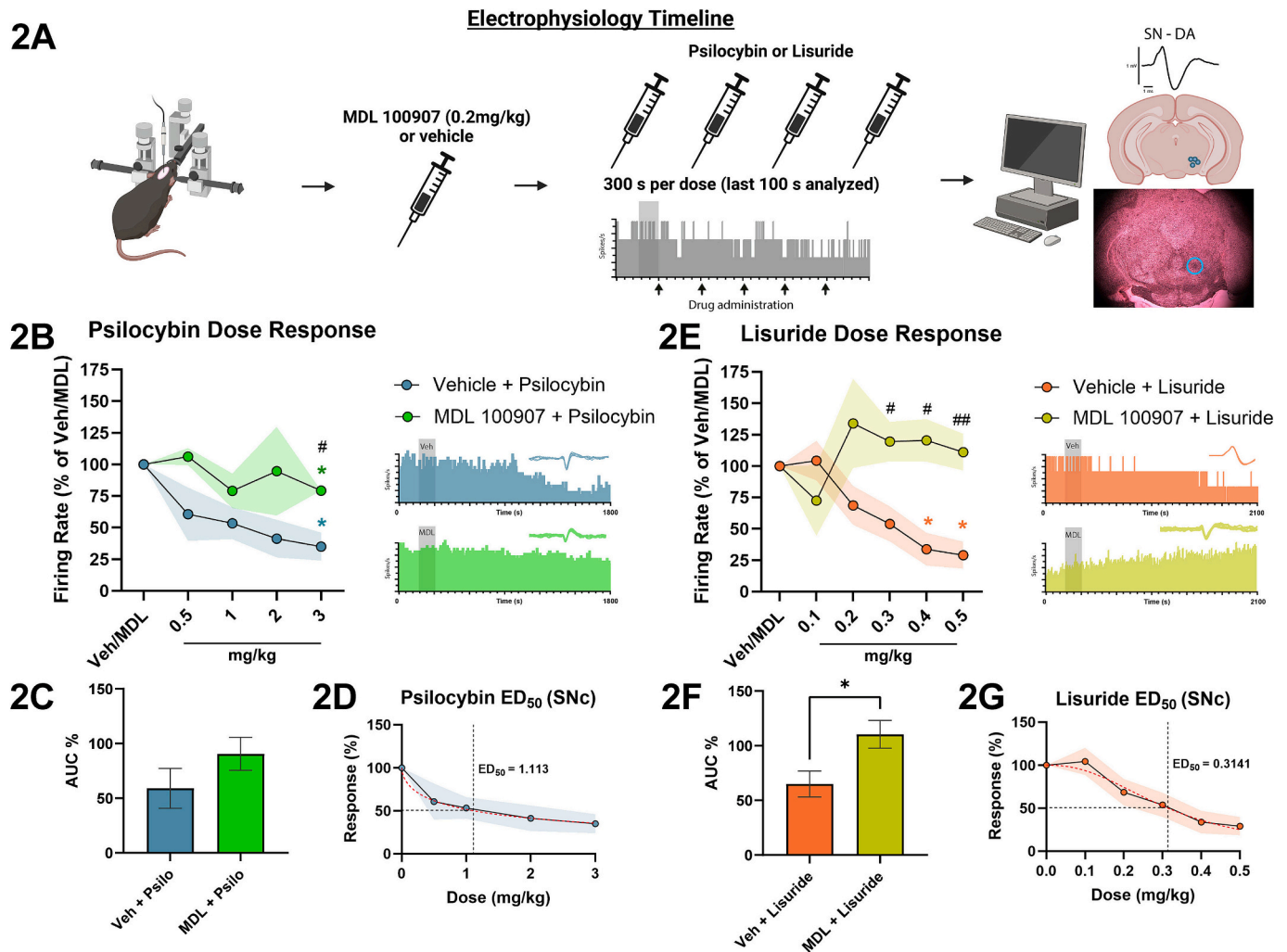


Fig. 2. Effects of psilocybin and lisuride on the firing activity of substantia nigra (SN) dopamine (DA) neurons. (2A) A schematic representation of the experimental timeline with the coronal section of the mouse brain, photomicrograph of the recording site in the SN and the typical waveform. Each dose response is accompanied with representative integrated firing rate histograms showing the acute response of neurons to psilocybin (0.5, 1, 2, and 3 mg/kg, i.p.) and lisuride (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg, i.p.). Change in firing rate is calculated by percentage (%) changed from vehicle (Veh) or MDL 100907 (MDL; 0.2 mg/kg, i.p.) administration. (2B–2C) Psilocybin ($n = 6$) at the dose of 3 mg/kg (i.p.) inhibits the firing rate of SN DA neurons, an effect that is partially blocked by MDL 100907 ($n = 3$). (2C) A comparison of the percentage (%) area under the curve (AUC) between vehicle + psilocybin and MDL 100907 + psilocybin. (2D) non-linear regression analysis (variable slope - 4 parameter; $R^2 = 0.99$) of the psilocybin dose response to obtain the ED₅₀. (2E–2F) Lisuride ($n = 8$) at the dose of 0.4 and 0.5 mg/kg (i.p.) inhibit the firing rate of SN DA neurons, blocked by MDL 100907 ($n = 3$). (2F) A comparison of the percentage (%) area under the curve (AUC) between vehicle + lisuride and MDL 100907 + lisuride. (2G) non-linear regression analysis (variable slope - 4 parameter; $R^2 = 0.98$) of the lisuride dose response to obtain the ED₅₀. * $p < 0.05$ compared to vehicle (Veh) treated mice, # $p < 0.05$, ## $p < 0.01$ compared to mice of the same dose group between conditions (e.g., vehicle + psilocybin 0.5 mg/kg vs. MDL 100907 + psilocybin 0.5 mg/kg). SN - substantia nigra, DA - dopamine, ED₅₀ - effective dose to cause 50 % of a response, AUC % - area under the curve percentage, Veh - vehicle, MDL - MDL 100907.

firing activity at the same doses (Fig. 2A). The substantia nigra pars compacta is a dopaminergic structure involved in movement regulation through its direct influence on the dorsal striatum and its indirect projections to the ventral tegmental area, which are associated with depression and addictive behaviors (Haber and Fudge, 1997; Winter et al., 2007). First, we tested the effects of vehicle followed by 0.5–3 mg/kg psilocybin in 6 SN DA neurons (one neuron per mouse) and then the effects of vehicle followed by 0.1–0.5 mg/kg lisuride in 8 SN DA neurons. We also investigated if MDL 100907 was able to block the effect of either psilocybin or lisuride on SN DA neurons.

Vehicle plus psilocybin (0.5–3 mg/kg) produced a dose-dependent decrease in SN DA firing frequency, which was not completely prevented by MDL 100907 (Two-way ANOVA for dose $F_{(2,48)} = 3.459$, $p = 0.0471$; pre-treatment $F_{(1, 7)} = 5.219$, $p = 0.0563$; interaction $F_{(4, 27)} = 1.374$, $p = 0.269$). The post-hoc analysis indicated that vehicle plus psilocybin (0.5–3 mg/kg) produced a significant decrease in SN DA

firing activity at the dose of 3 mg/kg ($p = 0.0198$; Fig. 2B). Moreover, MDL 100907 prevented this effect of psilocybin only at the dose of 3 mg/kg ($p = 0.01$; Fig. 2B). The AUC % did not significantly differ between vehicle plus psilocybin and MDL 100907 plus psilocybin, $t_{(7)} = 1.106$, $p = 0.1526$ (Fig. 2C). The ED₅₀ of psilocybin's inhibitory effect was 1.113 mg/kg (Fig. 2D).

Lisuride (0.1–0.5 mg/kg) produced a dose-dependent decrease in SN DA firing frequency that was prevented by MDL 100907 (Two-way ANOVA for dose $F_{(2,662)} = 2.065$, $p = 0.1397$; pre-treatment $F_{(1, 9)} = 6.941$, $p = 0.0272$; interaction $F_{(5, 41)} = 7.127$, $p = 0.0001$). The post-hoc analysis indicated that the lisuride significantly decreased SN DA activity at the dose of 0.4 mg/kg ($p = 0.0358$) and 0.5 mg/kg ($p = 0.0418$; Fig. 2E). However, in the MDL 100907 plus lisuride curve, none of the doses produced a decrease, indicating a strong prevention by the 5-HT_{2A} receptor antagonist. When we compared the dose response curves of vehicle plus lisuride vs MDL 100907 plus lisuride, we found

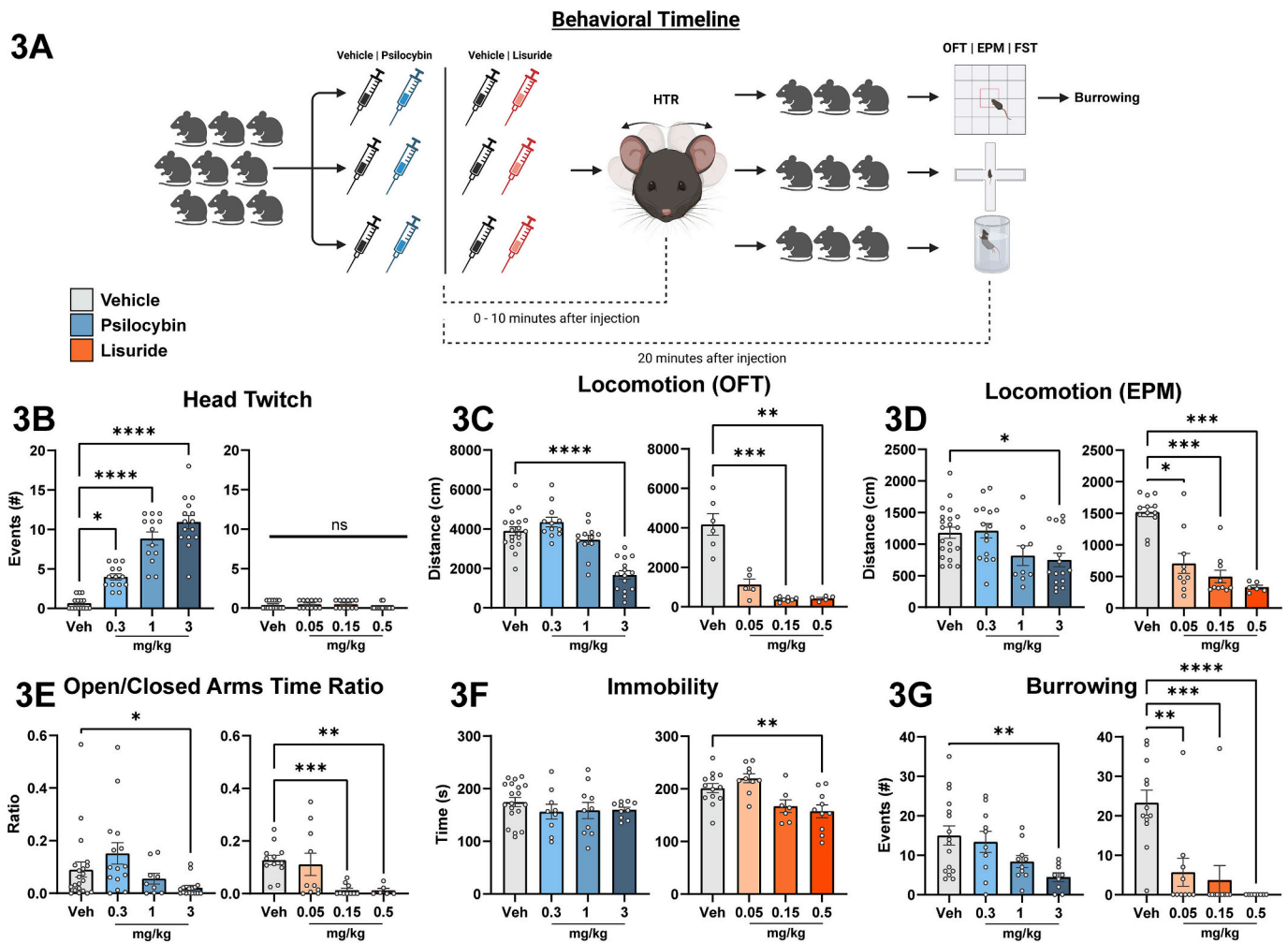


Fig. 3. Distinct and similar effects of psilocybin and lisuride on behavior. (3A) A schematic of the experimental timeline for the behavioral assays. (3B) Psilocybin dose-dependently increased the head twitch response, but not lisuride. (3C) Psilocybin decreased locomotor activity at the highest dose (3 mg/kg, i.p.) while lisuride did so at all doses. (3D) Psilocybin decreased locomotion in the EPM at the highest dose (3 mg/kg, i.p.). Lisuride decreased locomotor active in the EPM at all doses. (3E) Psilocybin induced an anxiogenic effect at 3 mg/kg (i.p.) by decreasing the ratio of time spent in the open arms. Lisuride produced a similar effect on the ratio of time spent in the open arms at 0.15 and 0.5 mg/kg (i.p.). (3F) Lisuride at its highest dose (0.5 mg/kg, i.p.) decreased immobility in the forced swim test, but not psilocybin. (3G) Only high dose of psilocybin (3 mg/kg, i.p.) decreased the number of burrowing events, whereas lisuride decreased burrowing events at all doses. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to vehicle (Veh) treated mice. HTR - head twitch response, OFT - open field test, EPM - elevated plus maze.

significant differences at the doses of 0.3 mg/kg ($p = 0.0236$), 0.4 mg/kg ($p = 0.0116$) and 0.5 mg/kg ($p = 0.0098$; Fig. 2E). Moreover, the AUC % showed that MDL 100907 plus lisuride dose response curve resulted in a significantly greater AUC % compared to vehicle plus lisuride dose response curve, $t_{(9)} = 2.136$, $p = 0.0307$ (Fig. 2F). The ED_{50} of lisuride's inhibitory effect was 0.3141 mg/kg (Fig. 2G).

SN DA neurons are known to discharge in bursts (Blythe et al., 2009; Grace and Bunney, 1984). We found that of 9 out of 14 SN DA neurons treated with vehicle, and 6 out of 6 treated with MDL 100907 exhibited bursting activity. Reports of the raw burst data and analysis for SN DA neurons, and changes caused by psilocybin or lisuride, can be found in the supplementary file (supplementary section 4: Table 3–4).

3.3. Psilocybin and lisuride both reduce locomotion, but lisuride does not induce HTR and promotes active coping behavior

As mentioned, lisuride is unlike psilocybin in that it is a 5-HT_{2A} receptor agonist without producing psychedelic effects in humans. Thus, we next compared the effects of both treatments on HTRs, a proxy for psychedelic-like effects in rodents (Halberstadt and Geyer, 2018). We

then investigated behavioral effects associated with mood, motivation, and motor function. Indeed, decreased DRN firing is understood to be an acute physiological correlate of antidepressant and/or anxiolytic effects (Gobbi and Blier, 2005; Lucki et al., 1994). Here, all mice were given i.p. injection of vehicle, psilocybin, or lisuride and then tested for HTRs for 10 min before being returned to their home cage. At 20 min post-injection, mice then had OFT, EPM or FST tests (Fig. 3A).

3.3.1. Head twitch response (HTR)

Psilocybin dose-dependently (0.3, 1, 3 mg/kg) increased the number of HTR events, $H_{(3)} = 45.18$, $p < 0.0001$, with statistically significant effects, compared to vehicle, at 0.3 mg/kg ($p = 0.0336$), 1 mg/kg ($p < 0.0001$), and 3 mg/kg ($p < 0.0001$). In comparison, lisuride did not induce HTR, $F_{(3, 43.61)} = 1.801$, $p = 0.1612$ (Fig. 3B).

3.3.2. Open Field Test (OFT)

Psilocybin administration significantly decreased the distance traveled (cm) in the OFT, $F_{(3, 54)} = 26.54$, $p < 0.0001$ with these effects driven by the highest dose, 3 mg/kg ($p < 0.0001$). Lisuride also had a significant impact on the distance traveled in the OFT, $H_{(3)} = 15.98$, $p =$

0.0011. Compared to vehicle, lisuride significantly decreased the distance traveled at the dose of 0.15 mg/kg ($p = 0.0005$) and 0.5 mg/kg ($p = 0.0097$; Fig. 3C). Further analyses of OFT parameters are reported in the supplementary file (supplementary section 3.1).

3.3.3. Elevated Plus Maze (EPM)

Psilocybin significantly decreased the distance traveled, $F_{(3, 57)} = 4.765$, $p = 0.0049$, and the open arm/closed arms ratio, $H_{(3)} = 13.47$, $p = 0.0037$, in the EPM with the clearest effects at the dose of 3 mg/kg ($p = 0.0107$; Fig. 3D and $p = 0.0356$; Fig. 3E). Significant decreases in the distance traveled, $H_{(3)} = 22.68$, $p < 0.0001$, and the open arm/closed arm ratio, $H_{(3)} = 17.35$, $p = 0.0006$, were also observed following

lisuride administration with significant effects on the former at all doses tested (0.05 mg/kg, $p = 0.0152$; 0.15 mg/kg, $p = 0.0005$; 0.5 mg/kg, $p = 0.0001$; Fig. 3D) and on the latter at the doses of 0.15 mg/kg ($p = 0.0009$) and 0.5 mg/kg ($p = 0.0078$; Fig. 3E). For further analysis of EPM parameters, see the supplementary file (supplementary section 3.2).

3.3.4. Forced Swim Test (FST)

As mentioned before, decreased DRN 5-HT activity has been linked to the antidepressant effects of SSRIs. Since both psilocybin and lisuride showed inhibitory effects of DRN 5-HT activity, we investigated whether psilocybin and lisuride impacted coping behavior in the FST by decreasing the time (s) spent immobile. Psilocybin showed no significant

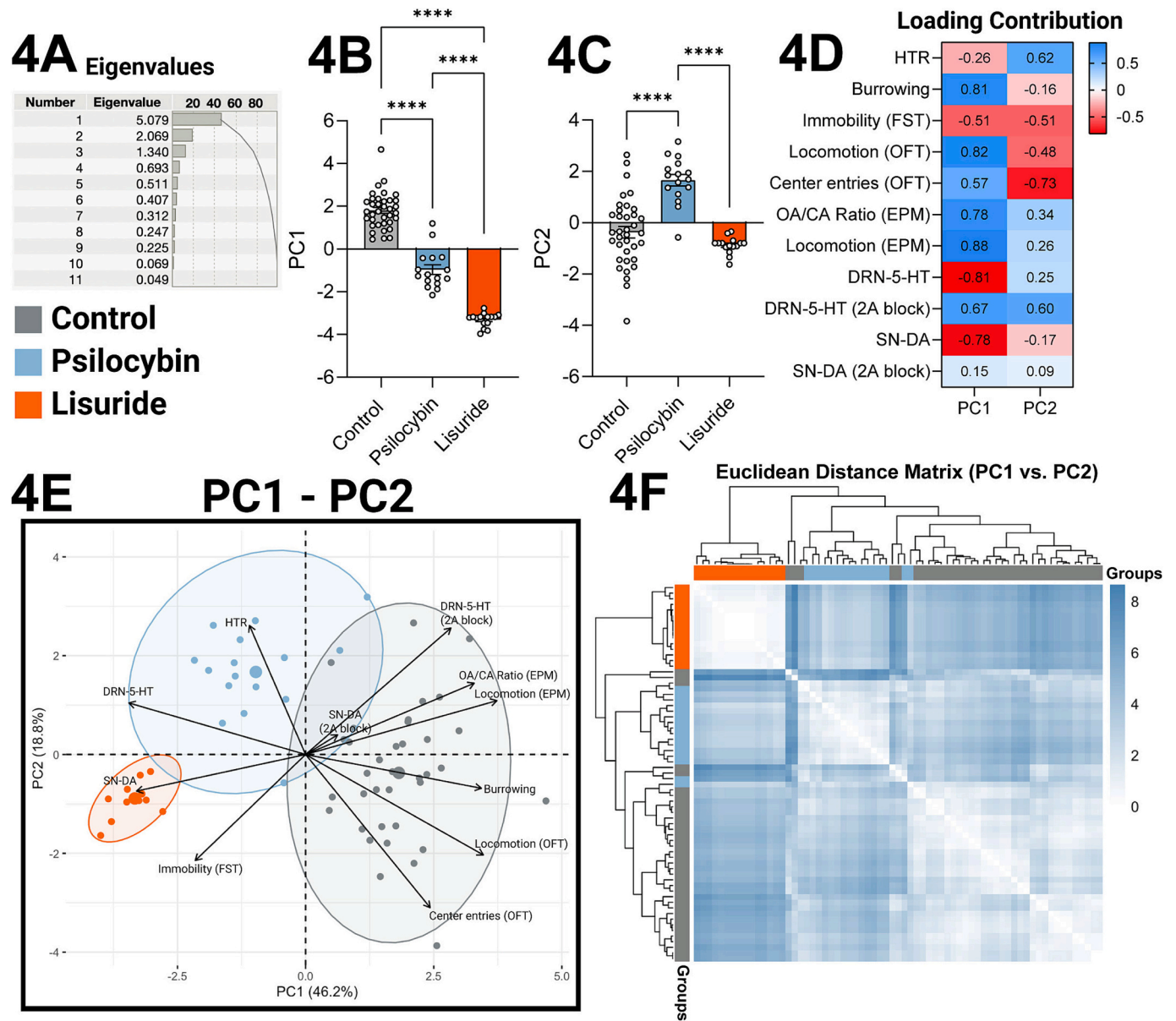


Fig. 4. Principal component analysis (PCA). Grey points represent the control group, blue points represent the psilocybin (3 mg/kg, i.p.) group, and orange points represent the lisuride (0.5 mg/kg, i.p.) group. (4A) Eigenvalues of the principal components (PC). (4B) PC1 completely separated treatment groups ($p < 0.0001$). (4C) Psilocybin group had significantly higher PC2 values than control ($p < 0.0001$) and lisuride ($p < 0.0001$). (4D) The correlation coefficient of the loading contributions of each parameter onto the PCs. (4E) The biplot for PC1-PC2, Arrows represent the correlation between the parameters and the principal component. (4F) Euclidean distance matrix visualized in a correlogram. Acronyms: HTR - head twitch response; SN-DA - substantia nigra dopamine inhibition; DRN-5-HT - dorsal raphe nucleus serotonin inhibition; SN-DA (2 A block) - substantia nigra dopamine inhibition blocked by MDL 100907; DRN-5-HT (2 A block) - dorsal raphe nucleus serotonin inhibition blocked by MDL 100907; EPM - elevated plus maze; OFT - open field test; FST - forced swim test; HTR - head twitch response; OA/CA (EPM) - open arms / closed arms time ratio in the elevated plus maze. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

changes in immobility time, $H_{(3)} = 3.339$, $p = 0.3423$. Lisuride, on the other hand, did elicit a significant decrease in immobility time, $F_{(3, 36)} = 8.013$, $p = 0.0003$. Post-hoc analysis revealed that compared to vehicle, lisuride at the dose of 0.5 mg/kg significantly reduced the immobility time ($p = 0.007$, Fig. 3F).

3.3.5. Burrowing

Psilocybin dose-dependently decreased the number of burrowing events, $H_{(3)} = 10.4$, $p = 0.0154$ (Fig. 3G) with significant effects at 3 mg/kg ($p = 0.0084$). Lisuride also decreased the number of burrowing events, $H_{(3)} = 24.48$, $p < 0.0001$, with significant effects at all doses tested: 0.05 mg/kg ($p = 0.0062$), 0.15 mg/kg ($p = 0.0002$) and 0.4 mg/kg ($p < 0.0001$; Fig. 3G).

3.4. Principal component analysis (PCA) reveals divergent effect profiles of psilocybin and lisuride

Next, to investigate whether psilocybin and lisuride converged or diverged in effect profile, we employed a dimensionality reduction approach that enables us to detect large scale differences in patterns of drug effects. We first used this approach to assess which parameters differentiated control from drug effects using principal component analysis (PCA). See the supplementary section 2.3 for pooling stratification and data processing and organization. We found that 2 principal components (PCs) were sufficient to explain approximately 67 % of the variance in the data, and thus we focused only on these 2 PCs (Fig. 4A). We found that for PC1 (Fig. 4B), treatment groups were significantly different, $F_{(2, 64)} = 243.4$, $p < 0.0001$. The post-hoc analysis indicated that PC1 completely separated all groups from each other (all group comparisons, $p < 0.0001$). PC2 (Fig. 4C) also revealed significant differences among treatment groups, $F_{(2, 64)} = 25.50$, $p < 0.0001$. The post-hoc analysis revealed that PC2 separated psilocybin from control ($p < 0.0001$), and lisuride ($p < 0.0001$). Next, we compared the correlation coefficients of the loading contribution of each parameter (Fig. 4D) onto PCs. Control mice had high PC1 values that were driven by strong contributions from locomotion in the EPM, locomotion in the OFT, burrowing, open arms/closed arms ratio in the EPM, and moderate contribution from 5-HT_{2A} mediation of the DRN firing activity, and center entries in the OFT. While lisuride treated mice had low PC1 values driven by strong contributions from DRN and SN firing activity, and moderate contribution from decreased immobility of the FST. For PC2, psilocybin treated mice had high values driven by moderate contributions from HTR and 5-HT_{2A} mediation of the DRN firing activity, and weak contribution from open arm/closed arm ratio, EPM locomotion, and DRN firing activity. While control and lisuride had low values driven by strong contribution of OFT center entries, moderate contribution of FST immobility and locomotion in the OFT, and weak contribution of burrowing, and SN firing activity. These findings were summarized and visualized in a PCA biplot (Fig. 4E), which displays the distribution of individual data points based on the combination of the PCs (PC1 and PC2) and highlights the clustering patterns according to treatment groups. We then further quantified the relationship between individual animals across treatment groups by calculating the Euclidean distances between data points in the PC1–PC2 coordinate spaces. These relationships were visualized as a correlogram (Fig. 4F). Results revealed that PC1 was sufficient for a clear segregation of psilocybin, lisuride, and control mice, reflecting the distinct behavioral and neurophysiological profiles of each group and indicating minimal overlap between them, thereby supporting the statistical robustness of the PCA-based classification.

4. Discussion

The goal of this work was to compare effects of psilocybin and lisuride on 5-HT and DA neuronal firing, as well as their effects on behavioral outcomes of locomotion, anxiety-like behaviors, coping

behaviors, and the HTR. Here, we highlight similarities of effect as well as important distinctions that provide insights into potential differences of mechanisms of action of effects.

4.1. Electrophysiological effects on DRN-5-HT neurons

Psilocybin and lisuride both inhibited the spontaneous firing activity of 5-HT neurons in a dose-dependent fashion. The current results are consistent with previous studies demonstrating that lisuride and psilocybin inhibit 5-HT neuron firing, ultimately leading to its complete cessation (De Gregorio et al., 2016; Fuxe and Calne, 1979; Rogawski and Aghajanian, 1979). The same effect has been reported for LSD and other psychedelics such as DMT (Aghajanian et al., 1968; Aghajanian et al., 1970; De Gregorio et al., 2016). Studies show that iontophoretically applied psychedelic compounds decrease 5-HT neuron firing, suggesting that this inhibition is mediated locally (De Gregorio et al., 2022; De Gregorio et al., 2021; De Gregorio et al., 2016; Rogawski and Aghajanian, 1979). Similarly, in the current investigation lisuride dose-dependently inhibited the firing activity of 5-HT neurons. Our results show that psilocybin-induced inhibition of DRN-5-HT firing activity was mediated by 5-HT_{2A} receptors. However, unlike psilocybin, MDL 100907 did not prevent lisuride-induced inhibition, implicating a different mechanism. Indeed, lisuride has been previously shown to increase the brain concentration of 5-HT, and to decrease levels of 5-hydroxytryptophan (5-HTP) and the 5-HT metabolite 5-hydroxy indoleacetic acid (Kehr, 1977). Moreover, recent work confirmed that lisuride is an ultrapotent 5-HT_{1A} receptor agonist in both *in vivo* and *in vitro* models (Egan et al., 1998; Glatfelter et al., 2024). Previous foundational work showed that 5-HT_{1A} autoreceptors directly inhibit DRN serotonergic firing, while 5-HT_{2A} receptors reduce activity indirectly via local GABA interneurons (Liu et al., 2000; Sprouse and Aghajanian, 1987). In this context, the psilocybin effect, though reversed by MDL100907, may involve secondary 5-HT_{1A} autoreceptor engagement, whereas lisuride likely acts more directly through 5-HT_{1A} receptors given its high affinity at this site, or through its impact on 5-HT (Kehr, 1977).

4.2. Electrophysiological effects on SN-DA neurons

Both compounds reduced DA firing activity in the SN, but the 5-HT_{2A} receptor antagonist MDL 100907 only partially prevented psilocybin's effects at the highest doses. On the contrary, MDL 100907 fully blocked lisuride's effects. Previous studies have shown that lisuride inhibits DA neuron firing in the ventral tegmental area (VTA), with these effects being prevented, but not reversed, by the D₂ receptor antagonist haloperidol (White and Wang, 1983). While this supports a role for 5-HT_{2A} receptors, it is notable that haloperidol also has some 5-HT_{2A} receptor inverse agonist properties, which could contribute to its ability to block lisuride's effects (Gaitonde et al., 2024). Nevertheless, lisuride is also a partial agonist at D₂ receptors, typically acting as an agonist in the A9 cell group of the SN pars compacta (Gessa, 1988). Depending on intrinsic DA concentration levels, it may function as an antagonist or produce only a submaximal response due to its lower intrinsic efficacy (Gessa, 1988; Pulvirenti and Koob, 1992). This raises the possibility that while 5-HT_{2A} receptors drive the primary effect, concurrent D₂ receptor engagement, particularly at autoreceptors, could modulate or fine-tune the response. Similarly, our previous studies showed that LSD inhibited DA neuron firing in the VTA at higher doses (>60 µg/kg) via a D₂/5-HT_{2A}/TAAR1 receptor-mediated mechanism (Qu et al., 2023), highlighting the potential for multi-receptor interactions in serotonergic modulation of DA systems.

Our results align with evidence that 5-HT_{2A} receptors can modulate dopaminergic autoreceptor function in the substantia nigra and ventral tegmental area. Specifically, 5-HT and the 5-HT₂ agonist DOI were shown to enhance D₂ receptor-mediated inhibition of dopamine neuron firing, an effect abolished by the selective 5-HT_{2A} antagonist

MDL100907 (and SB242084 for 5-HT_{2C}) (Olijslagers et al., 2004). This indicates that 5-HT_{2A} activation can augment D₂ autoreceptor-dependent suppression of DA activity, likely through both direct and indirect mechanisms. Within this framework, the complete blockade of lisuride's effect by MDL100907 suggests that its reduction of substantia nigra DA activity is mediated primarily through 5-HT_{2A}-dependent facilitation of D₂ autoreceptor signaling. In contrast, psilocybin's partial MDL100907 sensitivity implies additional receptor contributions beyond this 5-HT_{2A}-D₂ interaction.

4.3. Psychedelic-like effects

As previously reported, lisuride does not evoke a HTR even at higher doses (Gerber et al., 1985), while psilocybin dose-dependently increases it (Bruno et al., 2025; González-Maeso et al., 2007; Halberstadt et al., 2020; Halberstadt and Geyer, 2013; Halberstadt et al., 2011; Hesselgrave et al., 2021; Shahar et al., 2022; Shao et al., 2021; Singh et al., 2023). HTR is employed as a proxy for 5-HT_{2A} receptor-mediated psychedelic-like effects, suggesting that lisuride fails to induce such effects. Although it is known that lisuride is not a psychedelic compound (Herrmann et al., 1977), few reports indicate that lisuride may provoke hallucinosis in certain conditions, such as Parkinsonism and Shy-Drager syndrome (Lees and Bannister, 1981; Schachter et al., 1980). One study reported the onset of HTR in a bell-shaped fashion following lisuride administration (Darmani et al., 1994); however, this study was performed in the least shrew, limiting cross-species generalizability.

Psilocybin- and LSD-induced HTR are primarily due to their action at the 5-HT_{2A} receptor (Halberstadt et al., 2011), with some implications of 5-HT_{1A}, 5-HT_{2C}, and TAAR1 (Shahar et al., 2022). Lisuride, while also binding to 5-HT_{2A} and 5-HT_{1A} receptors shares partial D₂ agonism with LSD (Glatfelter et al., 2024), but likely differs in its degree of activity at these receptors leading to a lack of HTR. In fact pretreatment with WAY100635, a selective 5-HT_{1A} antagonist, does not facilitate HTR in lisuride, but potentiates LSD-induced HTR (Glatfelter et al., 2024); highlighting an important mechanistic distinction between lisuride and LSD. Our findings suggest that due to lisuride's unique effect profile, its 5-HT_{2A} receptor agonism isn't sufficient to induce HTR. Lisuride's inability to produce the HTR may be related to its action as a partial agonist at dopamine D₂ receptors (Newman-Tancredi et al., 2002; Pogorelov et al., 2023). Classic psychedelics activate the 5-HT_{2A} receptor, leading to increased glutamate release in cortical circuits, which is strongly implicated in the induction of HTR (Benvenha et al., 2018; De Gregorio et al., 2018; Szpregiel and Bysiek, 2024). However, the involvement of glutamatergic action is believed to be crucial for therapeutic action of psychedelics (De Gregorio et al., 2018). In contrast to psilocybin, lisuride's D₂ partial agonism could counteract the glutamatergic surge produced by 5-HT_{2A} receptor activation, thereby attenuating the behavioral expression of HTR (Tritsch and Sabatini, 2012). Additionally, dopamine D₂ receptors can directly modulate 5-HT_{2A} receptor function through receptor heteromerization. D₂ activation increases hallucinogen agonist affinity at 5-HT_{2A} while attenuating its inositol phosphate signaling pathway, suggesting cross-regulation at the receptor complex level (Albizu et al., 2011). This potential interaction highlights an important dopaminergic-glutamatergic regulatory mechanism that may underlie lisuride's distinct pharmacological profile compared to hallucinogenic 5-HT_{2A} agonists.

4.4. Effects of psilocybin and lisuride on coping behavior

At lisuride's maximal dose (0.5 mg/kg), it promoted active coping behavior in the FST by decreasing immobility time, whereas psilocybin (3 mg/kg) did not. The antidepressant-like effects of lisuride were reported by several groups even if the effects seem to be transient (Pogorelov et al., 2023; Qu et al., 2023). Interestingly, we did not expect that psilocybin would not have an effect in the FST. This negative result could be linked to the dose used or the time of exposure. Indeed, other

groups have found that psilocybin improved coping behavior in the FST (Moliner et al., 2023; Sekssaoui et al., 2024; Zhao et al., 2024). Ongoing investigations in our laboratory are attempting to understand this gap and to determine if psilocybin, like LSD, is more effective after repeated administration in rodents (De Gregorio et al., 2022).

Our findings suggest that psychedelic effects, reflected by HTR, are not a requisite for improvements in behavior, such as stress coping. Indeed, studies show that psilocybin retain antidepressant-like actions in chronic stress paradigms in mice even when 5-HT_{2A} receptor activity was blocked by ketanserin, despite complete suppression of HTR and other 5-HT_{2A} receptor physiological readouts (Hesselgrave et al., 2021). Similarly, reports demonstrated that psilocybin-induced antidepressant effects persisted in 5-HT_{2A} knockout mice, indicating that classical psychedelic signaling is not required for therapeutic benefit (Sekssaoui et al., 2024). Despite psilocybin failing to produce an antidepressant-like effect in the current study at the doses tested, lisuride reliably produces antidepressant-like responses without producing HTR, further supporting the idea that perceptual alterations are dissociable from therapeutic outcomes (Qu et al., 2023). On the contrary, the presence of HTR, indicative of 5-HT_{2A} receptor activity in psychedelics, does not reliably produce antidepressant-like effects. While cortical glutamate release downstream of 5-HT_{2A} activation is generally linked to antidepressant effects of psychedelics, our findings suggest that the context and balance of receptor interactions may be just as critical (De Gregorio et al., 2018). In this case, lisuride's partial D₂ agonism may shift the functional outcome of glutamatergic activity toward an antidepressant profile, whereas psilocybin's presumed glutamate increase alone is not sufficient to reduce immobility in the FST. Our findings, coupled with prior literature, reinforce the need to reconsider the prevailing assumption that psychedelic experiences are indispensable for therapeutic efficacy.

It is also important to note that our conclusions are based on the FST, which, while widely used for antidepressant screening, primarily captures behavioral coping strategies and does not encompass the full spectrum of depression-related phenotypes. Different paradigms, such as sucrose preference, novelty-suppressed feeding, or social interaction tests, engage distinct monoaminergic systems and neuronal circuits and may therefore yield different results (Gobbi et al., 2005; Meyer-olbersleben et al., 2020). Thus, the lack of antidepressant-like effects of psilocybin in the FST does not exclude the possibility of efficacy in other behavioral domains, and future studies should employ a battery of complementary assays to more comprehensively assess antidepressant potential associated with its monoaminergic impacts.

4.5. Locomotor impairments and Anxiogenic-like effects

We found that psilocybin and lisuride elicited a dose-dependent anxiogenic-like effect in the EPM test by reducing the ratio of time spent in the open arms. A previous study also identified an anxiogenic-like effect of 3 mg/kg psilocybin in the OFT, as measured by increased thigmotaxis (Fadahunsi et al., 2022). Despite the read-out of an anxiogenic-like effect by both lisuride and psilocybin, we also observed that both drugs elicited strong impairments of locomotion in both EPM and OFT, indicating a sedative-like effect. To control for the impacts on locomotion as confounds, ratios were calculated for OFT and EPM. These were time spent in the center to the total distance traveled in the OFT and open-arms time to open-arms entries in the EPM (see supplementary section 3.1 and 3.2). Here we find that dependent on the environment, psilocybin at 3 mg/kg remained anxiogenic in the OFT while lisuride did not. However, in the EPM, the effects are reverse in which lisuride at 0.15 mg/kg remained anxiogenic in the EPM, whereas psilocybin's effect was lost. Our findings suggest important contextual implications of the anxiogenic effects of psilocybin and lisuride.

Decreased locomotion strengthens the finding of lisuride's effect on coping behavior in the FST suggesting context specific effects. Similar to the results presented here, previous studies identified a sedative-like effect of psilocybin in rodents in the OFT (Chen et al., 2023;

Fadahunsi et al., 2022; Hesselgrave et al., 2021; Higgins et al., 2021), as measured by decreased locomotor activity, a phenotype that was exacerbated by 5-HT_{2A} receptor antagonism and thus not mediated by the 5-HT_{2A} receptor (Halberstadt et al., 2011; Hesselgrave et al., 2021; Higgins et al., 2021). Accordingly, psilocin, the active metabolite of psilocybin, has been shown in other studies to suppress locomotor activity and elicit thigmotaxis through 5-HT_{1A}/5-HT_{2C} receptor activation. Thus, the sedative-like effects observed following psilocybin administration are likely mediated by its rapid enzymatic conversion to psilocin, which subsequently engages 5-HT_{1A}/5-HT_{2C} receptors in addition to 5-HT_{2A} (Halberstadt et al., 2011; Halberstadt et al., 2009; Tylš et al., 2016). The sedative effect of lisuride and psilocybin was also associated to a decrease in burrowing, an OCD-like behavior, as recently reported (Brownstien et al., 2024). These positive effects call for more research to test these compounds as anti-OCD treatments.

4.6. Principal component analysis revealed distinct profiles

Our principal component analysis (PCA) clearly demonstrates that psilocybin and lisuride produce distinct neurophysiological and behavioral profiles. Psilocybin primarily engages serotonergic pathways via 5-HT_{2A} receptors, consistent with its psychedelic properties, while lisuride predominantly influences dopaminergic circuits and exhibits non-psychedelic, antidepressant-like effects.

The PCA robustly separated control, psilocybin, and lisuride groups, with minimal overlap. PC1 captured adaptive, baseline-like behaviors in control animals and dopaminergic modulation in lisuride-treated mice. PC2 selectively differentiated psilocybin, driven by serotonin-specific markers such as the head twitch response and 5-HT_{2A}-mediated firing in the dorsal raphe. These findings confirm that although both drugs act on 5-HT_{2A} receptors, they do not converge on similar effect profiles. Instead, psilocybin and lisuride recruit distinct neural systems, which may underlie their divergent behavioral outcomes and therapeutic potentials.

5. Conclusion

In conclusion, this study highlights key differences and similarities between the psychedelic psilocybin and the non-psychedelic lisuride in their effects on serotonergic and dopaminergic neuronal activity, and behavior. Both compounds decreased 5-HT and DA neuronal firing, yet the mechanisms underlying these effects diverged, with psilocybin primarily acting through 5-HT_{2A} receptors and lisuride through alternative pathways. Behaviorally, lisuride exhibited reduced immobility in the FST at its maximal dose, whereas psilocybin, at the doses tested did not. Both drugs reduced locomotion and exhibited anxiogenic-like effects, though their sedative-like properties complicated anxiety-related interpretations. Notably, psilocybin induced the HTR, whereas lisuride lacked this effect. These findings advance our understanding of the serotonergic and dopaminergic modulation underlying the distinct effects of psilocybin and lisuride, offering insights into their potential therapeutic applications and limitations. Further investigation is warranted to clarify these mechanisms and explore their implications for treating mood disorders, OCD, and other neuropsychiatric conditions.

CRedit authorship contribution statement

Brandon Richardson: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Antonio Inserra:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Michael Pileggi:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Thomas Prud'Homme:** Writing – review & editing, Methodology, Investigation, Data curation. **Vitor Bruno:** Writing – review & editing, Visualization, Software, Formal

analysis, Data curation. **Derek Wan-Yan-Chan:** Writing – review & editing, Methodology, Investigation, Data curation. **Ilia Shareghi-Ghareman:** Writing – review & editing, Investigation. **Sofia Nasini:** Writing – review & editing, Investigation. **Tadhg Strand:** Writing – review & editing, Investigation. **Marco Leyton:** Supervision. **Nahum Sonenberg:** Supervision. **Danilo De Gregorio:** Methodology, Conceptualization. **Jeffrey Sprouse:** Conceptualization. **Francis R. Bambico:** Supervision, Data curation. **Gabriella Gobbi:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology.

Ethical statement

The procedures were approved by the McGill University Ethics Committee and the McGill Comparative Medicine and Animal Resources Center (protocol #5764) and conducted in accordance with the Canadian Council on Animal Care Guidelines and the Canadian Institute of Health Research for Animal Care and Scientific Use.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnpbp.2025.111522>.

Data availability

Data will be made available on request.

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