The Hallucinogen DOI Reduces Low-Frequency Oscillations in Rat Prefrontal Cortex: Reversal by Antipsychotic Drugs

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Background: Perceptual and psychic alterations and thought disorder are fundamental elements of schizophrenia symptoms, a pathology associated with an abnormal macro- and microcircuitry of several brain areas including the prefrontal cortex (PFC). Alterations in information processing in PFC may partly underlie schizophrenia symptoms.

Methods: The 5-$HT_{2A/2C}$ agonist DOI and antipsychotic drugs were administered to anesthetized rats. Single unit and local field potential (LFP) extracellular recordings were made in medial PFC (mPFC). Electrolytic lesions were performed in the thalamic nuclei.

Results: DOI markedly disrupts cellular and network activity in rat PFC. DOI altered pyramidal discharge in mPFC (39% excited, 27% inhibited, 34% unaffected; n = 51). In all instances, DOI concurrently reduced low-frequency oscillations (.3–4 Hz; power spectrum: .25 ± .02 and .14 ± .01 μV^2 in basal conditions and after 50–300 μg/kg intravenous (IV) DOI, respectively; n = 51). Moreover, DOI disrupted the temporal association between the active phase of LFP and pyramidal discharge. Both effects were reversed by M100907 (5-HT_{2A} receptor antagonist) and were not attenuated by thalamic lesions, supporting an intracortical origin of the effects of DOI. The reduction in low-frequency oscillations induced by DOI was significantly reversed by the antipsychotic drugs haloperidol (.1–.2 mg/kg IV) and clozapine (1 mg/kg IV).

Conclusions: DOI disorganizes network activity in PFC, reducing low-frequency oscillations and desynchronizing pyramidal discharge from active phases of LFP. These effects may underlie DOI's psychotomimetic action. The reversal by clozapine and haloperidol indicates that antipsychotic drugs may reduce psychotic symptoms by normalizing an altered PFC function.

Key Words: 5-HT_{2A} receptors, EEG, local field potential, psychotomimetic agents, pyramidal neurons, schizophrenia

Schizophrenia is associated with anatomic, cellular, and neurochemical alterations of the prefrontal cortex (PFC) among other brain structures (1–5). The PFC is critically involved in many higher brain functions, including cognition, attention, and behavioral control (6,7) which are altered in schizophrenia patients (8).

A mesocortical dopaminergic hypoactivity is associated with the cognitive deficits and negative symptoms in schizophrenic patients (9,10). In contrast, subcortical (e.g., mesolimbic) dopaminergic hyperactivity has been suggested to mediate positive (psychotic) symptoms, such as delusions and hallucinations, in schizophrenia patients (11–13). These perceptual alterations in schizophrenia patients are sensitive to treatment with classical and atypical antipsychotic drugs. Blockade by these drugs of an overactive mesolimbic dopaminergic transmission may normalize an aberrant reward prediction induced by excessive dopaminergic transmission (14).

However, psychotic symptoms can be also evoked by nondopaminergic psychotomimetic agents, such as the noncompetitive N-methyl-*D*-aspartate receptor (NMDA-R) antagonists (15–19). Also, serotonergic agents such as lysergic acid diathylamine and related compounds, which are agonists of 5-HT_{2A} receptors, can produce perceptual and psychic alterations (20). DOI (1-[2,5-dimethoxy-4-iodophenyl-2-aminopropane]) is a partial 5-$HT_{2A/2C}$ agonist that evokes long-lasting alterations in consciousness and perception (20). DOI acts by overstimulating 5-HT_{2A} receptors, because its behavioral, neurochemical, and electrophysiologic effects are blocked by the selective 5-HT_{2A} receptor antagonist M100907 (21–23). However, the precise manner by which DOI evokes perceptual and psychic effects is not fully understood.

Activation of 5-HT_{2A} receptors by 5-HT or agonists elicits several electrophysiologic actions on cortical neurons recorded in vitro, increasing excitatory synaptic inputs (24,25) and changes in membrane properties, including membrane depolarization and reduction of the after-hyperpolarization that follows spike bursts (26,27). In vivo, 5-HT_{2A} receptor activation by endogenous 5-HT moderately increases pyramidal discharge (28,29), whereas systemic DOI administration evokes a dramatic increase in the firing rate of a subpopulation of PFC pyramidal neurons (23). However, despite the increasing knowledge of the cellular actions of hallucinogens, there is a lack of information concerning their actions at the network level.

We recently reported that the noncompetitive NMDA-R antagonist phencyclidine (PCP) markedly disrupts the cortical synchrony in the low-frequency range (.3–4 Hz) in rat PFC, an effect reversed by the antipsychotic drugs haloperidol (HAL) and clozapine (CLZ) (30). Here we extend these studies by showing that 1) DOI alters cortical synchrony in PFC similarly to PCP and 2) that this effect is also reversed by antipsychotic drug administration. Likewise, given previous reports suggesting an action of hallucinogens on thalamocortical 5-HT_{2A} receptors (25), we examined the dependence of the DOI's effect on the integrity of thalamocortical afferents to PFC.

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Methods and Materials

Animals

Male albino Wistar rats (250–320 g, Iffa Credo, Lyon, France) were kept in a controlled environment (12-hour light-dark cycle, 22 ± 2°C) with food and water provided ad libitum. Animal care followed the European Union regulations (O.J. of E.C. L358/1 18/12/1986).

Drugs and Reagents

Clozapine and DOI were obtained from Sigma/RBI (Natick, Massachusetts); M100907 [R-(+)-alpha-(2,3-dimethoxyphenil)-1-[4-fluorophenylethyl]-4-piperidinemethanol] (Lilly code LY 368675) was from Eli Lilly (Indianapolis, Indiana), and haloperidol (HAL) (intramuscular preparation) was from Laboratorios Esteve (Barcelona, Spain). Doses are expressed as free bases.

Electrophysiologic Experiments

Two sets of experiments were carried out. In the first series, we examined the effects of DOI on pyramidal cell firing in control and thalamic-lesioned rats. A preliminary report was published (23). The stored data corresponding to the neurons included in that report were reanalyzed to examine the effect of DOI on 1) burst firing, 2) local field potentials (LFP), and 3) temporal association between pyramidal discharge and LFP. Subsequently, a second series of experiments was carried out to examine the effects of antipsychotic drugs and M100907 on DOI-induced changes on LFP.

Single-unit extracellular recordings of pyramidal neurons were performed as previously described (23) in chloral hydrate–anesthetized rats. Pyramidal neurons were recorded extracellularly with glass micropipettes filled with 2 mol/L NaCl. The signal was amplified with a Neurodata IR283 (Cygnus Technology, Delaware Water Gap, Pennsylvania), postamplified and filtered with a Cibertec amplifier (Madrid, Spain) and computed online using a DAT 1401plus interface system Spike2 software (CED, Cambridge, United Kingdom). In the first series of experiments, LFPs were obtained by digitally filtering the signal using a band-pass filter at .1–60 Hz; LFPs in the experiments assessing the effects of antipsychotic drugs were obtained by online band-pass filtering the signal from the recording electrode as described (30).

Descents were carried out at anteroposterior (AP) +3.2 to +3.4, lateral (L) −5 to −1.0, dorsoventral (DV) −1.1 to 4.8 below the brain surface. To identify layer V–VI pyramidal neurons, stimulating electrodes were placed in two mPFC-innervated midbrain nuclei, the ventral tegmental area and the dorsal raphe nucleus (coordinates: dorsal raphe, AP −7.8, L −3.1, DV −6.8 with an angle of 30°; ventral tegmental area, AP −6.0, L −.5, DV −8.2) and were stimulated at .15–2 mA, .2 msec square pulses, .9 Hz to evoke antidromic spikes in pyramidal neurons of the mPFC. All recorded units were identified by antidromic activation and collision extinction with spontaneously occurring spikes (31). Only one recording per rat was performed (unit and/or LFP). In some cases, recording electrodes were filled with Pontamine sky blue to verify the recording site. Brain sections were stained with neutral red, according to standard procedures.

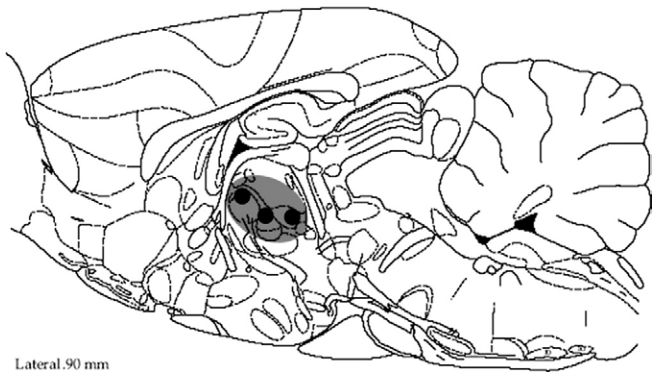


Figure 1. Sagittal view of the rat brain showing a schematic representation of the location of the tip of bipolar electrodes used to deliver electrolytic lesions in the thalamus. Stereotaxic coordinates for the three locations (black dots, from left to right) were as follows: 1) AP –1.8, L −.7, DV −5.7, 2) AP −2.7, L −.7, DV −6.3, and 3) AP −3.6, L −.7, DV −6.5, to target the mediodorsal and centromedial nuclei. The tip of electrodes was peeled off (~.5 mm), and poles were slightly separated (~.5 mm) to affect a larger tissue area. The shaded area shows the average extent of thalamic lesions. All rats showed extensive destruction of the centromedial and mediodorsal nuclei and also of the paracentral and paratenial nuclei. Additionally, most animals exhibited moderate to severe lesions of the anteromedial, centrolateral, parafascicular paraventricular, and reuniens nuclei, which also project to medial prefrontal cortex. Images of the actual thalamic lesions can be seen in Puig *et al.* (23). AP, anteroposterior; L, lateral; DV, dorsoventral.

Table 1. Increase in Activity of Pyramidal Neurons Produced by Systemic DOI Administration

	Basal	DOI
Firing rate (spikes/sec)	1.37 ± .48	5.80 ± .86[b]
% of spikes fired in bursts	52 ± 4	60 ± 4
Spikes in burst in 2 min	94 ± 39	460 ± 93[b]
Mean number of spikes per burst	2.13 ± .06	2.37 ± .08[a]
Number of bursts in 2 min	39 ± 15	181 ± 31[b]
Burst duration (msec)	14.43 ± 2.70	27.53 ± 2.99[b]
Interspike interval in bursts (msec)	11.92 ± 1.26	19.47 ± 1.19[b]
n	18	18

Data are means ± SEM.
[a] $p < .0005$.
[b] $p < .00001$.

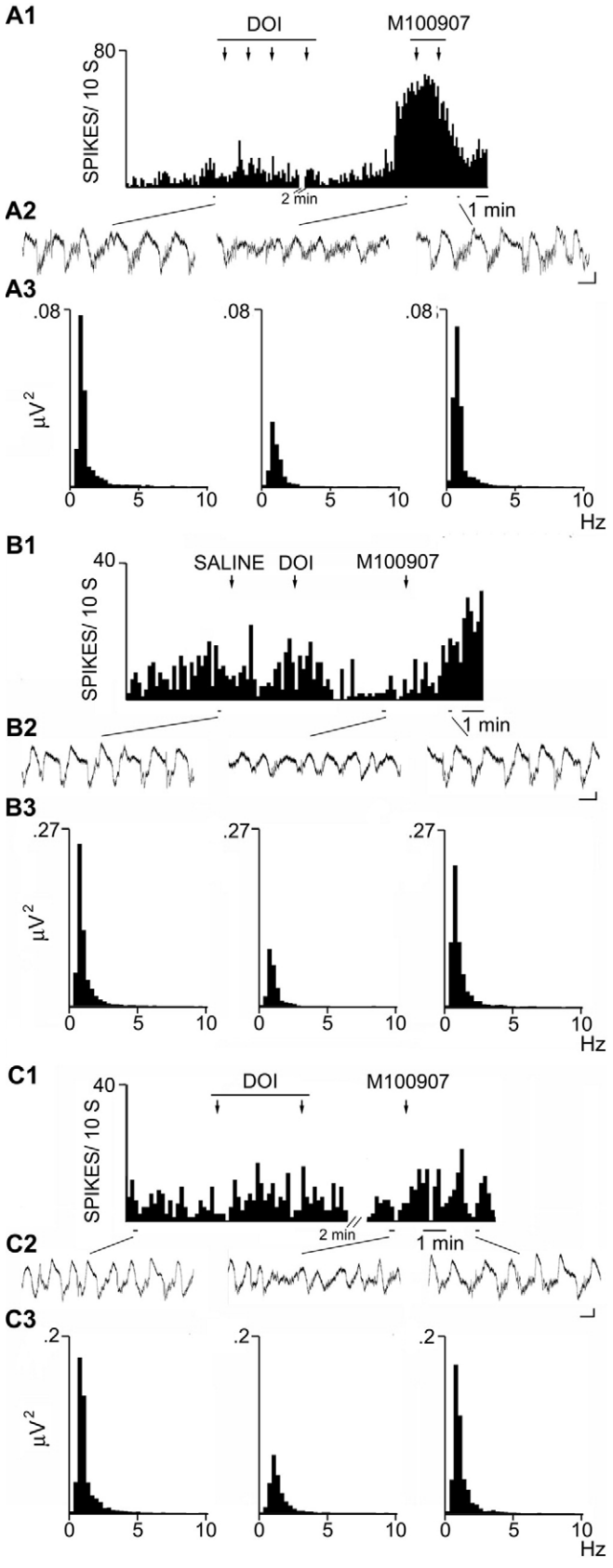
Thalamic Lesions and Histological Examinations

Electrolytic lesions of the several thalamic nuclei projecting to the mPFC (32,33) were performed by passing 1.5-mA (2 pulses of 10 sec each; Grass Technologies (Quincy, Massachusetts) stimulation unit S48 connected to a Grass SIU 5 stimulus isolation unit) at three localizations: 1) AP −1.8, L −.7, DV −5.7, 2) AP −2.7, L −.7, DV −6.3, and 3) AP −3.6, L −.7, DV −6.5 (Figure 1). The

Table 2. Reduction of the Activity of Pyramidal Neurons Produced by Systemic DOI Administration

	Basal	DOI
Firing rate (spikes/s)	1.08 ± .32	.24 ± .07[a]
% of spikes fired in bursts	46 ± 3	23 ± 7
Spikes in burst in 2 min	65 ± 24	8 ± 3[a]
Mean number of spikes per burst	2.16 ± .06	2.03 ± 0.02 ($n = 8$)
Number of bursts in 2 min	30 ± 11	4 ± 2[b]
Burst duration (msec)	16.28 ± 3.07 ($n = 8$)	10.42 ± 1.36[a]
Interspike interval in bursts (msec)	13.68 ± 2.08 ($n = 8$)	10.14 ± 1.26[a]
n	12	12

Data are means ± SEM.
[a] $p < .05$.
[b] $p < .0005$.



tip of electrodes was peeled off (~.5 mm), and poles were slightly separated (~.5 mm) to affect a larger tissue area.

At the end of the experiments, rats were killed by an overdose of anesthetic. Lesioned animals were examined in the same way. Brains were postfixed, sagittally sectioned (80 μm), and stained with Neutral Red.

Data and Statistical Analysis

Changes in firing rate or burst firing in pyramidal neurons were assessed using analysis of variance (ANOVA) or paired Student's *t* test, as appropriate. Values were quantified over 2 min in the baseline condition and after drug administration. Neurons were considered to respond to drugs if firing rate was altered ± 30% from baseline. Burst analysis was carried out using the method of Laviolette *et al*. (34). Briefly, a burst episode was defined as the occurrence of two or more spikes with an interspike interval <45 msec.

Power spectra were constructed using Fast Fourier Transforms (FFT) of 1-min signal intervals corresponding to baseline, DOI, and DOI + antipsychotics or M100907 time periods with a resolution of .3 Hz (FFT size of 8192). Data are given as area under the curve of the power spectrum between .3 and 4 Hz.

The temporal coincidence of discharged spikes with the active phase of low-frequency oscillations was examined (1 min for each treatment) with a custom-made script (Spike 2), as reported elsewhere (30). Briefly, the mean LFP voltage value was calculated for 1-min periods in basal conditions and after drug administration and the number of spikes discharged below and above this mean value (e.g., active and inactive LFP phases) were computed. Data are expressed as the mean SEM. Statistical significance has been set at $p < .05$ (two-tailed).

Results

Effects of DOI on Pyramidal Neuron Activity in mPFC

The effects of intravenous (IV) administration of DOI on the discharge rate of pyramidal neurons in the rat mPFC have been previously described (23). Here we extend our analysis of these data by showing the effect of DOI on burst firing and LFP. In the subgroup of units in which firing rate was increased by DOI

Figure 2. Simultaneous effect of DOI administration on pyramidal firing rate and low-frequency oscillations in medial prefrontal cortex (mPFC). Panels **A**, **B**, and **C** show the integrated firing rate histograms **(A1, B1, C1)**, local field potentials (LFP; **A2, B2, C2**), and the corresponding power spectra **(A3, B3, C3)** of three representative experiments assessing the simultaneous effect of the hallucinogen DOI (5-$HT_{2A/2C}$ agonist) and its reversal by the selective 5-HT_{2A} antagonist M100907 on single-unit activity and low-frequency oscillations in mPFC. Short lines below the integrated firing rate histograms denote the 10-sec periods corresponding to the LFP shown below. Neurons were classified according to their response to IV DOI administration as excited **(A)**, inhibited **(B),** or unaffected **(C). (A1–A3)** The unit in A1 had firing rates of .9, 5.0, and 1.6 spikes/sec in basal conditions, after intravenous (IV) DOI (50–300 μg/Kg) and after M100907 (.1–.4 mg/Kg), respectively. DOI simultaneously reduced the LFP **(A2)** and the corresponding power spectrum **(A3)** to 46% of basal and M100907 reversed this value to 138% of basal. **(B1–B3)** Example of a unit **(B1)** inhibited by DOI (.2 mg/kg IV) with a firing rate of .8, .3, and 2.0 spikes/sec in basal conditions and after DOI and M100907 (.1 mg/Kg), respectively. **B2** and **B3** show, respectively, the LFP simultaneously recorded and the corresponding power spectra. Note the similar effect of DOI on cortical synchrony in this unit and the unit shown in **A. (C1–C3)** Lack of a significant of DOI on the firing rate of a pyramidal neuron in mPFC in parallel with a reduction of low-frequency oscillations recorded simultaneously, similar to those observed in the above two examples. This unit had firing rates of .4, .4, and .8 spikes/sec during basal, DOI (.2 mg/ Kg) and M100907 (.1 mg/Kg) periods, respectively.

(.05–0.3 mg/kg IV; $n = 18$), a parallel increase in the number of spikes fired in bursts, the total number of bursts and the duration of burst episodes was observed (Table 1). Conversely, DOI administration (.05–.3 mg/kg IV) reduced burst firing in the units whose discharge rate was inhibited ($n = 12$; Table 2).

Reduction of Low-Frequency Oscillations in mPFC by DOI

In parallel with the effect on pyramidal discharge, DOI administration markedly reduced the amplitude of low-frequency (.3–4 Hz) oscillations in the mPFC. This change occurred in all experiments conducted (power spectrum: .25 ± .02 and .14 ± .01 μV^2 in basal conditions and after DOI administration, respectively; $p < .0005$; $n = 51$; one experiment per rat) irrespectively of whether DOI increased, decreased or left unaffected the firing rate of the recorded unit. Figure 2 shows representative examples of the effect of DOI in three experiments illustrating the simultaneous action on the pyramidal discharge and on the low-frequency oscillation in mPFC. Two-way ANOVA of the power spectra revealed a significant effect of DOI in all subgroups [excited, inhibited, and unaffected by DOI; $F(2,48) = .27$, nonsignificant effect of the subgroup or DOI × subgroup interaction; Figure 3A).

The effect of the subsequent administration of the selective 5-HT_{2A} receptor antagonist M100907 was examined in 23 experiments. The administration of this agent (.1–.5 mg/kg IV) completely reversed the reduction in low-frequency oscillations induced by the previous administration of DOI (Figures 2 and 3). One-way repeated-measures ANOVA showed a significant effect of the treatment [$F(2,44) = 38.8$, $p < .00001$] with significant post hoc differences between DOI and baseline and between DOI + M100907 and DOI (Figure 3B). The administration of M100907 alone (.2 mg/kg IV) did not alter the amplitude of low-frequency oscillations during the first 5 min postadministration (baseline: .28 ± .06 μV^2, M100907: .26 ± .06 μV^2; $n = 5$ rats; n.s.). In some units, M100907 administration after DOI increased the firing rate above baseline (Figures 2B1, 4B1, and 4C1). However, M100907 given alone did not significantly change the firing rate (baseline: .56 ± .31 spikes/sec; M100907: .60 ± .39 spikes/sec; $n = 5$; n.s.). Supplement 1 shows representative examples of the action of DOI (.25 mg/kg IV) and M100907 (.2 and 1 mg/kg IV) on low-frequency oscillation in mPFC. Note the long-lasting effect of DOI and the absence of effect of M100907.

Effect of Thalamic Lesions on DOI-Induced Effects on Low-Frequency Oscillations

Rats were subjected to electrolytic lesions as described in Methods and Materials. All brain sections from lesioned rats showed extensive destruction of the centromedial and mediodorsal nuclei and also of the paracentral and paratenial nuclei. Additionally, most animals exhibited moderate to severe lesions of the anteromedial, centrolateral, parafascicular paraventricular and reuniens nuclei, which also project to the cingulate and limbic subdivisions of the mPFC. Figure 1 shows the location of stimulating electrodes and the average lesioned area.

DOI administration (.05–.3 mg/kg IV) reduced low-frequency oscillations in both experimental groups with a larger effect in thalamic-lesioned rats. Two-way ANOVA showed a significant effect of DOI [$F(1,58) = 74.3$, $p < .00001$) and the lesion [$F(1,58) = 5.15$, $p < .03$] with significant post hoc differences of baseline and post-DOI values between naïve and lesioned rats. Hence, baseline power spectra in naïve and lesioned rats were, respectively, .25 ± .02 and .19 ± .02 μV^2, and post-DOI values were .14 ± .01 and .06 ± .02 μV^2 ($n = 51$ and 9, respectively).

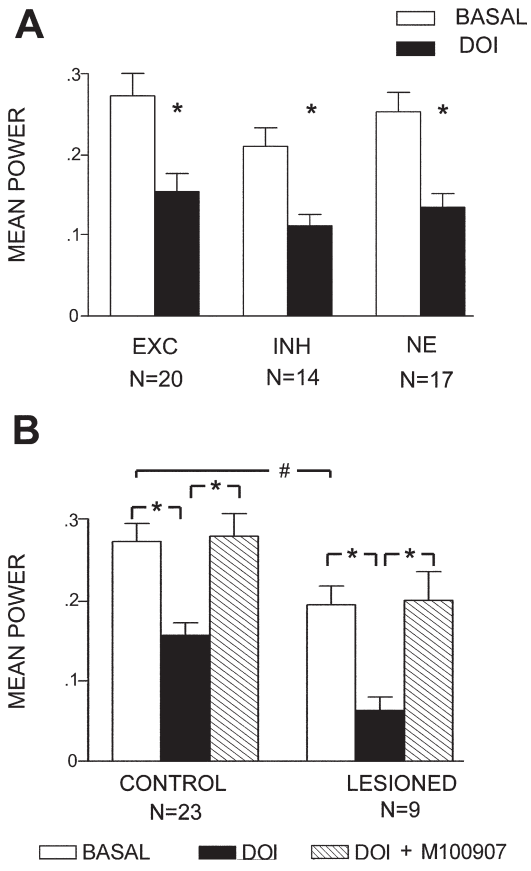
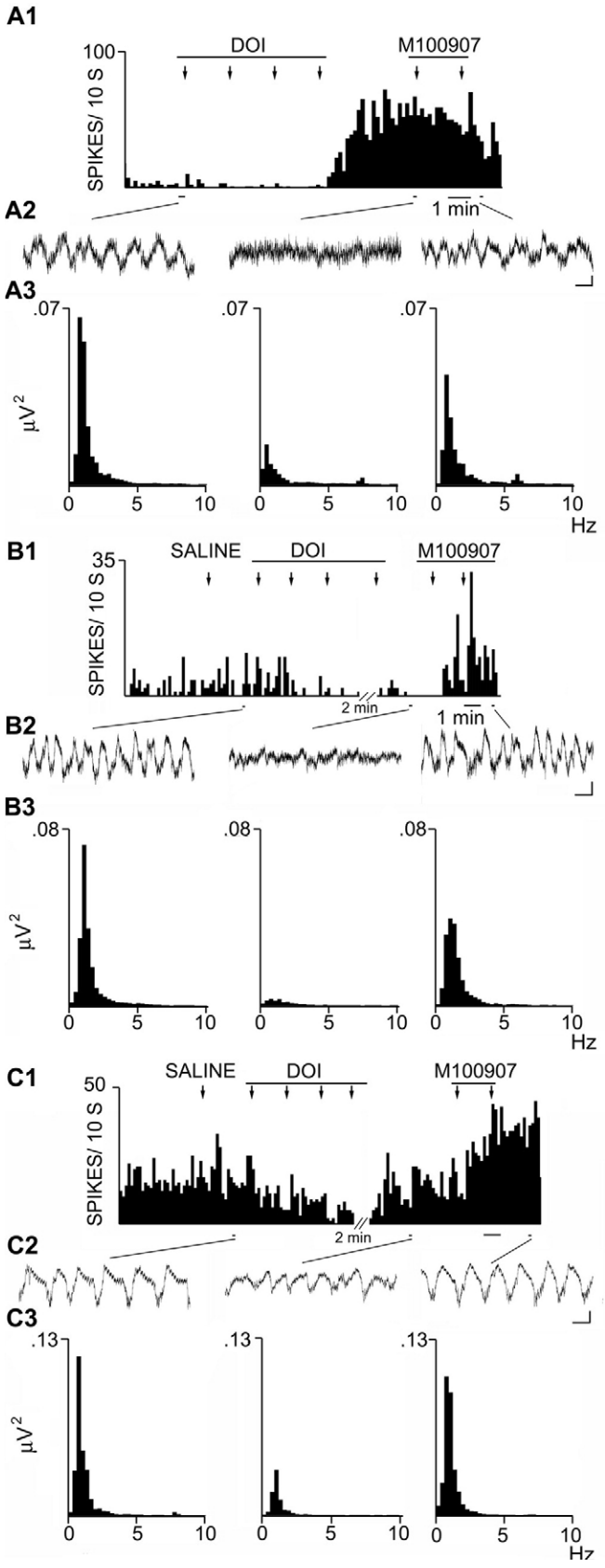


Figure 3. Effect of DOI on low frequency oscillations in medial prefrontal cortex (mPFC). **(A)** Bar graph showing the reduction of low-frequency oscillations (power spectra) evoked by DOI in experiments in which the simultaneous single-unit recordings showed an excitation (EXC), inhibition (INH), or no effect (NE) of DOI on pyramidal cell firing ($n = 20$, 14, and 17, respectively; one experiment per rat). **(B)** Bar graph showing the suppressing effect of DOI on low-frequency oscillations (power spectra) in naïve and thalamic-lesioned rats. Shown is also the reversal of this effect by the selective 5-HT_{2A} receptor antagonist M00907. Data corresponding to 23 naïve rats and 9 lesioned rats (those treated with DOI and subsequent M100907 administration). * $p < .0001$, # $p < .02$.

The selective 5-HT_{2A} receptor antagonist M100907 also reversed the DOI-induced reduction of the power of low-frequency oscillations in the mPFC of lesioned rats. M100907 reversal was examined in nine experiments in lesioned rats (Figure 3B). One-way ANOVA revealed a significant effect of M100907 [$F(2,16) = 21.9$, $p < .00001$] with significant post hoc differences between baseline and DOI periods and between DOI and DOI + M100907 periods (Figure 3B). Figure 4 shows individual examples of three experiments in which the extracellularly recorded units were excited (A), inhibited (B), or unaffected (C) by IV DOI administration in thalamic-lesioned rats.

Loss of the Temporal Association Between LFP and Discharged Spikes

The NMDA-R antagonist PCP evoked a loss of the temporal association between the discharged spikes and the active phase of the LFP in anesthetized rats (30). Here we examined whether DOI could induce a similar desynchronization of network activity in PFC. Of the described 23 experiments, 6 were excluded from this analysis because of insufficient number of spikes, either



during basal or post-DOI periods. Three experiments in lesioned rats were excluded for the same reason.

Figure 5 shows the LFP and spikes of pyramidal neurons simultaneously recorded before (A1, B) and after DOI administration (A2). In baseline conditions, most spikes were discharged during the active phase of the LFP (i.e., below mean voltage value; 91 ± 2% in control rats; $n = 17$; Figure 5C). DOI administration reduced this proportion in naïve rats and in those with thalamic lesions. This effect was antagonized by the subsequent administration of M100907 in both groups. One-way ANOVA of the effect of DOI and M100907 in naïve rats showed a significant effect of treatment [$F(2,32) = 14.1$, $p < .00001$] with significant differences between DOI versus baseline and DOI + M100907 versus DOI alone. DOI was equally effective in thalamic-lesioned rats [$F(2,10) = 12.5$, $p < .002$]. Two-way ANOVA of the data in naïve and lesioned rats indicated a significant effect of the treatment [$F(2,42) = 24.9$, $p < .0001$] with no significant effects of lesion or lesion x treatment interaction (Figure 5C).

Antipsychotic Drug Reversal of DOI-Induced Alterations of Low-Frequency Oscillations in mPFC

The classical and atypical antipsychotic drugs haloperidol (.1–.2 mg/kg IV) and clozapine (1 mg/kg IV), respectively, induced a full (clozapine) or partial (haloperidol) reversal of the DOI-evoked reduction in the power of low-frequency oscillations in mPFC. Neither drug altered the power spectrum by itself (clozapine 1 mg/kg IV: 100 ± 8% of basal, $n = 5$; haloperidol .1 mg/kg IV 104 ± 5% of basal, $n = 4$). Figure 6 shows two representative examples of the effect of DOI and the subsequent administration of clozapine (Figure 6A) and haloperidol (Figure 6B) on LFP. A saline injection did not alter the amplitude of LFP by itself nor altered the suppression induced by DOI when administered at a time similar to that of antipsychotic drugs (Supplement 2). In these experiments, DOI induced a reduction of the power spectrum to 44% ± 5% of baseline ($p < .00001$; n = 13). One-way ANOVA of the data corresponding to each treatment group revealed a significant effect of drug [$F(2,8) = 47.3$, $p < .00001$, $n = 5$ for clozapine; $F(2,14) = 89.1$, $p < .0001$, $n = 8$

Figure 4. Effect of thalamic lesions on DOI-induced alterations of cortical activity. Panels **A, B,** and **C** show the integrated firing rate histograms **(A1, B1, C1)**, local field potentials (LFP; **A2, B2, C2**), and the corresponding power spectra **(A3, B3, C3)** of three representative experiments assessing the simultaneous effect of the hallucinogen DOI (5-$HT_{2A/2C}$ agonist) and its reversal by the selective 5-HT_{2A} antagonist M100907 on single-unit activity and low-frequency oscillations in medial prefrontal cortex (mPFC). Short lines below the integrated firing rate histograms denote the 10-sec periods corresponding to the LFP shown below. Neurons were classified according to their response to intravenous (IV) DOI administration as excited **(A)**, inhibited **(B)**, or unaffected **(C). (A1–A3)** The unit in A1 had firing rates of .2, 5.4, and 3.1 spikes/sec in basal conditions, after IV DOI (50–300 μg/ Kg) and after M100907 (.25–.5 mg/Kg), respectively. DOI simultaneously reduced the LFP **(A2)** and the corresponding power spectrum **(A3)** to 17% of basal and M100907 reversed this value to 73% of basal. **(B1–B3)** Example of a unit **(B1)** inhibited by DOI (.2 mg/kg IV) with a firing rate of .4, 0, and 1.1 spikes/sec in basal conditions and after DOI (50–200 μg/Kg) and M100907 (.2–.4 mg/Kg), respectively. **B2** and **B3** show respectively the LFP simultaneously recorded and the corresponding power spectra. Note the similar effect of DOI on cortical synchrony in this unit and the unit shown in panel **A**. **(C1–C3)** Lack of a significant of DOI on the firing rate of a pyramidal neuron in mPFC in parallel with a reduction of low-frequency oscillations recorded simultaneously, similar to those observed in the above two examples. This unit had firing rates of 1.6, 1.5, and 3.5 spikes/sec during basal, DOI (50–300 μg/Kg) and M100907 (.1–.2 mg/Kg) periods, respectively. LFP scale: ordinate 1 mV, abscissa 1 sec.

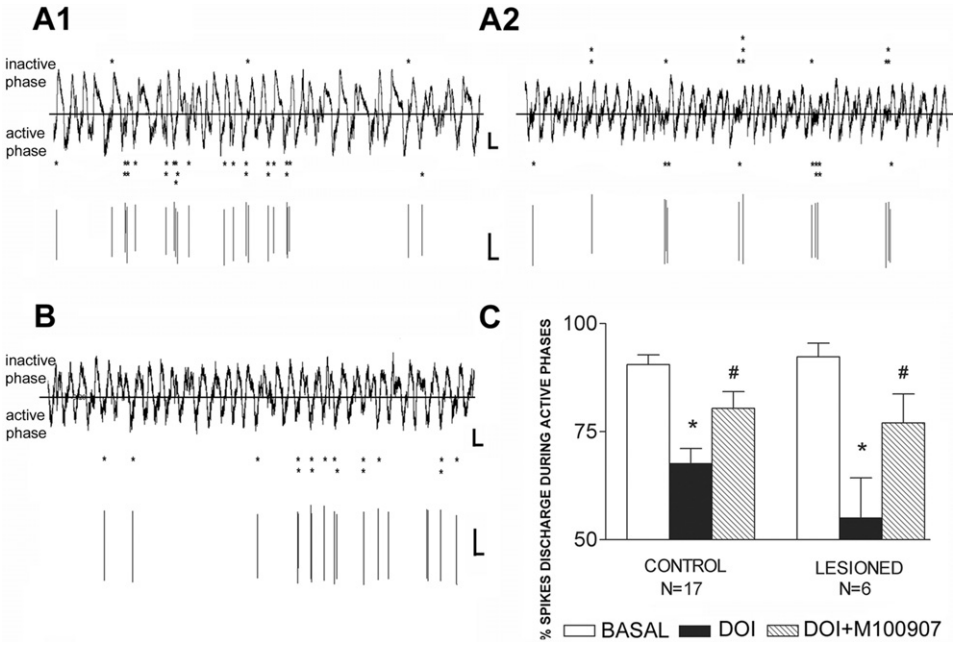


Figure 5. Synchronization of the discharge of pyramidal neurons with active phases of the .3–4 Hz oscillations recorded in medial prefrontal cortex (mPFC) in naïve **(A)** and thalamic-lesioned rats **(B). (A1)** In baseline conditions, extracellularly recorded spikes occur mainly during active phases (downward infections in the figure). In this example, the percentage of spikes discharged during active phases was 89%. Each asterisk shows the temporal coincidence of a discharged spike and the active (down) and inactive (up) phases of the corresponding local field potential (LFP). **(A2)** After DOI administration, this value was reduced to 48%. **(B1)** Note the persistence of slow oscillations in mPFC after the lesion of the centromedial and mediodorsal nuclei of the thalamus. In this particular example, 100% of the spikes were discharged during active phases of LFP. Scale: abscissa 1 sec, ordinate 1 mV. **(C)** Bar graph showing the effect of DOI on the percentage of spikes discharged during active phases of LFP in control and thalamic lesioned rats. M100907 reversed the reduction in this proportion in both groups of rats. * $p < .05$ vs. basal, # $p < .05$ vs. DOI alone (post–analysis of variance test).

for haloperidol] with significant post hoc differences between DOI versus baseline and DOI + antipsychotic versus DOI.

Discussion

This study sheds new light on the neurobiological basis of the psychotomimetic effect of the 5-$HT_{2A/2C}$ receptor agonist DOI. Previous in vitro studies showed that DOI increased spontaneous and evoked EPSCs in layer V pyramidal neurons of the rat mPFC (24,25). Subsequent in vivo studies indicated that systemic DOI administration markedly altered the firing rate of pyramidal neurons with an overall increase in discharge (23). Likewise, DOI increased high-frequency network activity in rat mPFC recorded in vitro (35). Here we show that DOI additionally disrupts cortical activity by reducing low-frequency oscillations (.3–4 Hz) and by desynchronizing pyramidal discharge from active phases of slow oscillations. Moreover, DOI altered bursting activity of pyramidal neurons, in parallel with the change in overall firing rate. These network actions of DOI are similar to those of PCP (30) and may underlie the perceptual and psychic effects of DOI. Moreover, as observed with PCP, the disruption in cortical network synchrony was reversed by classical (HAL) and atypical (CLZ) antipsychotic drugs.

Effect of DOI on Low-Frequency Oscillations in mPFC

Slow (<1 Hz) and delta (1–4 Hz) oscillations recorded in the electroencephalogram (EEG) or extracellularly in deeply anesthetized animals are similar to the physiologic changes in cortical activity during slow-wave sleep (36). These oscillations play an important role in the disconnection of the brain from external afferent sources, information processing and memory consolidation during sleep. Slow oscillatory activity reflects alternating periods of activity and silence ("up" and "down") of cortico-thalamo-cortical networks that result from synchronized changes in membrane potential and synaptic activity of neuronal ensembles (36–38). "Up" states are accompanied by persistent cortical activity that resembles that recorded during behavioral activation. Hence, simultaneous recordings of LFP and intracellular activity of neocortical neurons reveal a close temporal association between neuronal activity and active phases of the LFP, together with an increased occurrence of high-frequency (20–100 Hz) rhythms during active phases (39). Delta rhythms are generated in thalamocortical neurons due to the interplay of two intrinsic properties, the hyperpolarization-activated cation current (I_h) and the transient low-threshold Ca^{2+} current (I_T) (36). In periods of reduced cortical inputs, thalamocortical cells become deeply hyperpolarized and display spontaneous and self-sustained delta oscillations (36). However, slow (<1 Hz) spontaneous transitions between "up" and "down" states can be evoked in vitro in cortical slices (40), in agreement with their persistence in cats with thalamic lesions (41). This supports an intracortical origin of slow oscillations, yet some contribution of thalamocortical inputs has been observed (42). The moderate decrease of basal power spectra in rats with thalamic lesions agrees with previous data in cats (41) and suggests an important contribution of cortically generated slow oscillations to the low-frequency activity recorded in mPFC. However, because lesions affected primarily thalamic nuclei projecting to PFC, delta rhythms generated in other nuclei may perhaps reach the PFC indirectly, via intracortical connectivity (43).

The reversal by M100907 of DOI's actions indicates the participation of 5-HT_{2A} receptors. DOI was equally effective in control rats and in those with thalamic lesions, which supports that 5-HT_{2A} receptors involved in these effects are intracortical. This view agrees with recent observations obtained with LSD in a mouse line (htr2A−/−:Emx1-Cre+/−) after selective rescue of neocortical 5-HT_{2A} receptors (44). It also agrees with the 5-HT-mediated facilitation of synaptic activity in PFC through pyramidal 5-HT_{2A} receptors in mPFC (45). Overall, these observations do not support previous views on the role of putative thalamocortical 5-HT_{2A} receptors as mediators of the hallucinogen action (25,46).

In all experiments (n = 51) simultaneously examining the effect of DOI on pyramidal discharge and LFP, DOI reduced power spectra, irrespective of the effect on firing rate of the recorded unit. Interestingly, DOI desynchronized the pyramidal discharge rate from the active phases of LFP, which are temporally coincident with depolarized ("up") periods of neuronal activity in resting conditions (39). To our knowledge, the effect

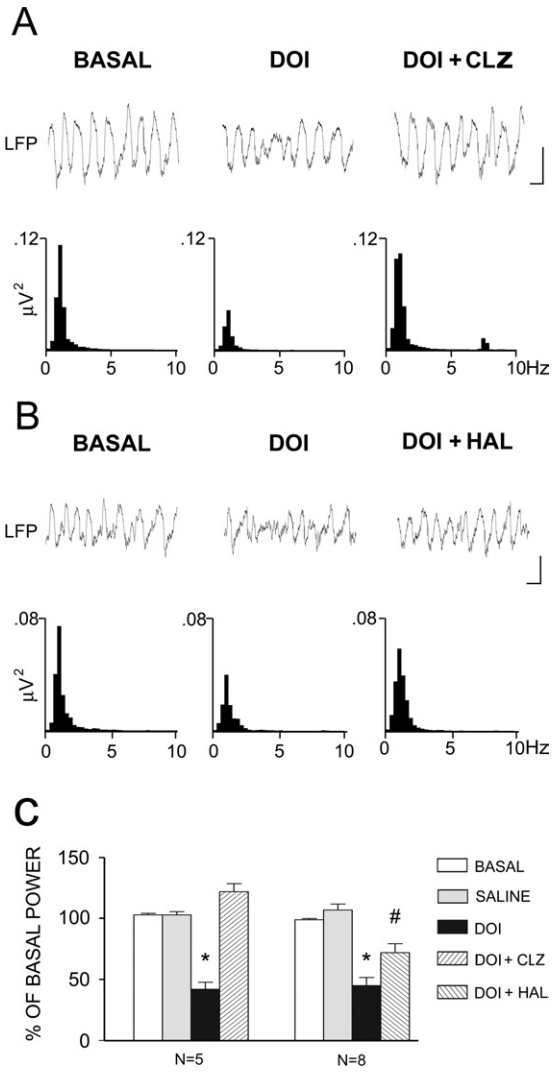


Figure 6. Reversal of the DOI-induced reduction in low-frequency oscillations by antipsychotic drugs. **(A and B)** Effect of intravenous (IV) .25 mg/kg DOI in two representative experiments and its reversal by the subsequent administration of 1 mg/kg IV clozapine (CLZ) **(A)** and .1 + .1 mg/kg IV haloperidol (HAL) **(B). (C)** shows the effect of DOI and the two antipsychotic drugs on low-frequency oscillations. LFP scale: abscissa 1 sec, ordinate 1 mV.

of DOI on pyramidal membrane properties has not been reported, yet 5-HT or DOB (DOI analog) depolarized pyramidal neurons and reduced slow AHP (I_{sAHP}) via 5-HT_{2A}-dependent activation of calcium-activated potassium currents (26,27). Given the large proportion of mPFC pyramidal and GABAergic neurons expressing 5-HT_{2A} receptors (51% and 34%, respectively in the recording area) (47), DOI's effect on cortical networks may derive from a depolarizing action in such a large neuronal proportion, thus altering the physiologic association between individual ("up" and "down" states) and population (LFP) measures. It is conceivable that a proportion of 5-HT_{2A} receptor-containing cells become depolarized by DOI and can fire action potentials, whereas DOI-insensitive neurons may still be in a hyperpolarized ("down") state. Likewise, the increased number of spikes discharged in burst episodes induced by DOI in excited neurons may additionally contribute to expand the altered activity to other units in the network. These dissimilar effects of DOI on PFC neurons may deeply alter network synchrony and reduce the amplitude of slow oscillations.

The PFC exerts a top-down control of neuronal activity in subcortical structures via descending excitatory axons (7,43). Therefore, DOI-induced alterations in network activity in mPFC may subsequently alter the activity of other brain areas, as observed with midbrain dopaminergic and serotonergic neurons (22,48–50).

Antipsychotic Reversal

Interestingly, HAL and CLZ attenuated the DOI-induced alteration in low-frequency oscillations, an effect possibly related to the ability of these dugs to attenuate/suppress psychotic symptoms in schizophrenic patients. CLZ shows high affinity for 5-HT_{2A} receptors (51–53), and it is likely that its reversal of DOI-induced alterations derives from a competitive displacement of DOI from 5-HT_{2A} receptors.

HAL was somewhat less effective than CLZ, yet its reversal was comparable to that produced by the same doses of HAL and CLZ on PCP effects in mPFC (30). HAL has lower affinity than CLZ for 5-HT_{2A} receptors (52,53) and does not occupy a substantial proportion of 5-HT_{2A} receptors in rat cortex at the dose used (54). Therefore, it is likely that its antagonism of DOI's actions is not mediated at receptor level and may involve actions in local or distal networks (or both). In basal conditions, HAL administration does not increase DA release in mPFC, possibly because of a low endogenous DA D2 autoreceptor tone (55). However, in a stimulated condition, such as after DOI administration (50,56,57) HAL may further increase PFC DA release by blocking a high DA tone on autoreceptors, leading to the activation of postsynaptic DA D1 receptors and, subsequently, to inhibition of pyramidal neuron activity. In support of this view, ventral tegmental area stimulation excited fast spiking interneurons and concurrently inhibited PFC pyramidal neurons (58). Also, DA D1 receptor stimulation reversed DOI-induced alterations in mPFC pyramidal neurons in vitro (35). Likewise, subcortical blockade of DA D2 receptors may also help to normalize information processing through cortico-limbic circuits feeding back to mPFC. Indeed, mPFC and VTA oscillatory activity appears to be tightly coupled (59,60).

Relevance to the Pathophysiology and Treatment of Schizophrenia

Numerous studies reported EEG abnormalities in schizophrenia patients that are often discordant or overtly contradictory (61). Alterations in high-frequency oscillations (beta, gamma) during the performance of specific tasks, thought to underlie cognitive deficits, have also been reported (62–65). Alterations in low-frequency oscillations may also be relevant, given the involvement of slow oscillations in cognitive processes, in particular, memory consolidation (66–68).

A reduced delta power has been found in schizophrenia patients during sleep (69–71). Interestingly, the reduction in delta and theta waves was present in patients with positive (psychotic) symptoms and not in those with mostly negative symptoms (72). Similar changes have been reported in healthy individuals during hallucinatory experience with ayahuasca, a South American beverage for which the active component is N,N-dymethyltryptamine, a 5-HT_{2A} agonist (73). This suggests that hallucinations may be associated to dysfunctional cortical processing, involving, among other actions, a reduction of cortical synchrony in the low-frequency range, as suggested by the effects of DOI.

The use of anesthesia prevents to establish a direct link between the observed changes and the psychotomimetic action of DOI. Hence, further studies are necessary to examine the effect of hallucinogens on cortical networks in awake animals. Moreover, the developmental and neuropathologic alterations in schizophrenia (1) cannot be modeled by the administration of psychoactive drugs even though these mimic certain symptoms of the illness. Despite these limitations, our observations provide new, relevant information on the neurobiological basis of hallucinations and may have a heuristic value in schizophrenia research, as an experimental model in drug discovery.

Indeed, DOI and PCP had strikingly similar effects on PFC network activity, despite their different primary pharmacologic and cellular targets. Both agents altered pyramidal firing rate similarly (39%–45% neurons excited, 27%–39% neurons inhibited, 22%–34% neurons unaffected) and evoked a comparable reduction of low-frequency oscillations (30, this study). Interestingly, the mitotoxic agent methylazoxymethanol, used as a neurodevelopmental model of schizophrenia, also reduced low-frequency oscillations in the PFC (74). Moreover, the alterations in network activity produced by DOI and PCP were sensitive to treatment with HAL and CLZ (30, this study), which supports their relevance in schizophrenia research.

Despite these common actions in PFC, DOI and PCP may differ in their primary site(s) of action. DOI possibly has a more restricted action in neocortex given the localization of 5-HT_{2A} receptors, whereas PCP may alter the activity of cortical and subcortical areas rich in NMDA receptors. Thus, DOI increased cortical *c-fos* expression (75), whereas PCP increased *c-fos* in cortical and subcortical (mainly thalamic) areas (30).

Further work should examine the effects of DOI on network activity in awake rats to establish direct comparisons with EEG measures in drug-naïve and treated schizophrenia patients.

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