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Research paper

Comparison of electroencephalogram (EEG) response to MDPV versus the hallucinogenic drugs MK-801 and ketamine in rats

Ibrahim M. Shokry[a,b,1], Vikash Sinha[a,1], Guilherme Da Silva[a], Sol-be Park[a], John J. Callanan[b], Rui Tao[a,*]

[a] Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA
[b] Ross University School of Veterinary Medicine, St. Kitts, Saint Kitts and Nevis

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ABSTRACT

Synthetic cathinones, often marketed as 'bath salts', have been reported to induce an excited delirium syndrome with characteristic symptoms such as paranoid, hallucination and even aggression. 3,4-Methylenedioxypyrovalerone (MDPV), a norepinephrine-dopamine reuptake inhibitor (NDRI), is one of the psychoactive ingredients in bath salts. The present study utilized cortical EEG and brain microdialysis in rats to compare the effects of MDPV (0.25, 1 and 2 mg/kg, i.p.) with the hallucinogenic drugs MK-801 (0.05, 0.1 and 0.5 mg/kg, i.p.) and ketamine (5, 15 and 25 mg/kg, i.p.). Results revealed that MDPV similar to MK-801 and ketamine caused a dose-dependent increase in the cortical EEG synchronization. In addition, all three drugs produced an increase in DA efflux in the prefrontal cortex (FCx). However, there existed difference between the three drugs. In contrast to MDPV, MK-801 and ketamine had only moderate or little effects on DA efflux in the nucleus accumbens (NAcc). Except for ketamine, the effects of MDPV and MK-801 on EEG synchronization were blocked by the D_1 receptor antagonist SCH23990 (0.1 mg/kg, i.p.) and D_2 receptor antagonist sulpiride (100 mg/kg, i.p.). SCH23990 or sulpiride had no effect on ketamine-induced increases in EEG synchronization. In summary, the present comparative studies suggest that DA in the FCx, but unlikely the NAcc, exerts a critical role in increasing EEG synchronization associated with the excited delirium syndrome. Neural circuits consisting of glutamatergic and GABAergic neurons responsible for the hallucinogenic effect are discussed in the context of hyperdopamine and dysconnection theories for hallucinatory behaviors.

1. Introduction

3,4-Methylenedioxypyrovalerone (MDPV) is one of the main psychoactive ingredients in bath salts abused in the US (Ross et al., 2012). Abuse of MDPV causes paranoid, hallucinatory delirium and aggressive behavior (Stevenson and Tuddenham, 2014; Desharnais et al., 2017; John et al., 2017; Diestelmann et al., 2018). These signs and symptoms are collectively described as an excited delirium syndrome (Penders et al., 2012; Karch, 2015), or broadly reported as acute psychosis (Diestelmann et al., 2018). Besides MDPV, other bath salts and psychostimulants were also reported to cause this kind of psychotic behaviors that usually last hours or days and thus have been defined as a transient psychosis (McKetin et al., 2016; Stiles et al., 2016). In this manuscript, the terms "excited delirium syndrome", "acute psychosis" and "transient psychosis" will be interchangeably used for the sake of convenience in an essay description. Clinically, the transient psychotic effects of MDPV can be pharmacologically relieved by typical antipsychotics commonly prescribed for patients with schizophrenia (Penders et al., 2012; Mangewala et al., 2013). Although little is known about the antipsychotic effect on MDPV abuse, the working mechanisms for schizophrenia patients lead to suggest that the hallucinatory behaviors may be due to an aberrant of dopaminergic activity in the striatum and nucleus accumbens (NAcc), showing increases in DA turnover (hyperdopamine) and upregulation in D_2 receptors (Thompson et al., 2013; Kubota et al., 2017). In this context, dopaminergic abnormalities in the striatum and NAcc are believed to be involved in not only the hallucinatory psychosis of schizophrenia, but also transient psychosis caused by psychostimulants (Mori et al., 2016; Thanos et al., 2017), including MDPV (Baumann et al., 2017).

MK-801 and ketamine are two hallucinogenic drugs commonly used

* Corresponding author at: Charles E. Schmidt College of Medicine, Department of Biomedical Science, Florida Atlantic University, 777 Glades Road, Boca Raton, FL 33431, USA.
E-mail address: rtao@health.fau.edu (R. Tao).
[1] IMS and VS had equal contribution to this work.

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to reproduce a schizophrenia-like response in animals (Hiyoshi et al., 2014; Furth et al., 2017) and humans (Light et al., 2017; Grent-'t-Jong et al., 2018). Both drugs act as NMDA receptor antagonists to disrupt the inhibitory transmission from GABAergic neurons to pyramidal neurons (Szabadics et al., 2001; Kirschstein and Kohling, 2009; Okimura et al., 2015; Gerashchenko et al., 2018). D_1 and D_2 receptors are found in the interneurons (Santana and Artigas, 2017) and pyramidal neurons (Mocci et al., 2014; Clarkson et al., 2017). Through these receptors, DA imposes a powerful control over the microcircuits (Xu and Yao, 2010). Neurologically, MDPV acts as a norepinephrine-dopamine reuptake inhibitor (NDRI). Interestingly, NDRIs exert regionally selective effects in the brain. For instance, Moghaddam and Bunney (1989) reported that cocaine at a small dose in rats had no effects on DA in the prefrontal cortex (FCx) whereas the same dose markedly evoked DA elevation in the NAcc. In the study of a dose-response relationship from five male rhesus macaques, Jedema et al. (2014) found that AMPH caused a steeper slope in the striatum relative to the FCx. In addition to these psychostimulants, regionally differential effects also occur to non-psychostimulants. For instance, nomifensine administration caused greater increases in the striatum and NAcc than the cortical DA (Mazei et al., 2002).

Patients with hallucinatory psychosis, including both idiopathic and iatrogenic disorders, were found to have abnormalities in the electroencephalogram [EEG; (Mattia and Moreton, 1986, Lee et al., 2006, Grent-'t-Jong et al., 2018)]. EEG is one of the accessible approaches to reveal the hallucinatory psychosis elicited by the hallucinogenic drugs MK-801 and ketamine in laboratory settings (Pinault, 2008; Cordon et al., 2015; Furth et al., 2017; Slovik et al., 2017). However, little is known about an EEG response to MDPV. The present study was designed to compare effects of MDPV with MK-801 and ketamine on EEG synchronization associated with hallucinations of the transient psychosis. The involvement of D_1 and D_2 receptors was examined with SCH23990 and sulpiride, respectively. Furthermore, we compared the effects of MDPV with MK-801 and ketamine on DA efflux in the NAcc and FCx to evaluate the regional difference in response to these drugs. Some of these data have been reported in a preliminary form (Shokry et al., 2018).

2. Materials and methods

2.1. Animals

Male adult Sprague-Dawley rats weighing 300–350 g were purchased from the Charles River Laboratories (Raleigh, NC, USA) and housed under standard conditions (lights-on from 07:00–19:00, humidity at 40–70%). Food and water were continuously available. All procedures involving animals were carried out in accordance with the NIH guidelines and preapproved by the Florida Atlantic University and Ross University Veterinary School Institutional Animal Care and Use Committees (IACUC).

2.2. Chemicals

(+)MK-801 and SCH23990 (SCH) were purchased from Tocris Bioscience (Ellisville, MO, USA). Sulpiride and ketamine were purchased from Sigma (St. Louis, MO, USA). MDPV was courtly provided by the NIDA drug supply program (Bethesda, MD). Drugs were dissolved in sterile 0.9% NaCl and administered IP in a volume of 1 mL/kg of body weight. In this study, drugs were examined at a dose range from 0.5–2 mg/kg for MDPV, 0.05–0.5 mg/kg for MK-801, and 5–25 mg/kg for ketamine. SCH at 0.1 mg/kg was used to block effect of D_1 receptors and sulpiride at 100 mg/kg to block effect of D_2 receptors. Antagonistic dosages used in this study were based on previous work (Pruitt et al., 1995; Banasikowski and Beninger, 2012).

2.3. Electroencephalogram (EEG)

Electrodes were pre-implanted on animal skulls according to a surgical procedure preapproved by the Florida Atlantic University and Ross University Veterinary School Institutional Animal Care and Use Committees (IACUC). Briefly, rats were anesthetized with a combination of xylazine (4 mg/kg i.p.) and ketamine (80 mg/kg i.p.). A stainless steel electrode was anchored on the skull over the frontal cortex (AP +2 mm relative to the bregma, ML 2 mm relative to the midline) as positive and reference electrodes for surface EEG recording. A third electrode was implanted on the occipital bone over the cerebellum to serve as the negative electrode. After surgery, rats were housed individually and allowed a week for recovery. The day before EEG recording, animals were placed overnight in a Faraday chamber shielded with a metal mesh for blocking electromagnetic interference from surrounding environment. On following day, recording began with 30 min of basal measurements and then 120 min of post-drug recordings. During the recording sessions, animals were gently handled for at least 30-s at 5 min intervals to ensure that rats were at the wakeful state.

Electroencephalograms were analyzed off-line. Each 15-min datum was the mean of triplicate samples consisting of the first, middle and last 5 min EEG activity. The sample size was 10-s. Thus, each animal generated 2 basal levels and 8 post-drug data. The cut-off frequencies performed using the Chart 7.01 software were set at 1–4 Hz as a δ band, 4–8 Hz as a θ band, 8–12 Hz as an α band, 12–30 Hz as a β band, and 30–100 Hz as a γ band. Raw traces were transformed into power spectral density (PSD; μV^2/Hz) using the Fast Fourier Transform (FFT). Two basal PSDs were averaged as baseline. Data were normalized as percent (%) changes of the baseline values.

2.4. Microdialysis

New groups of animals were assigned for microdialysis. Guide cannulas (10 mm in length 22-gauge stainless steel tubing; Small Parts, FL, USA) were surgically implanted in place one week prior to microdialysis experiments. A microdialysis probe was 2.5 mm in length × 0.2 mm in diameter of a semipermeable hollow fiber (molecular weight cut-off 18 kD; Spectrum Laboratories Inc., CA, USA). The in vitro recovery on DA was 45.3% (± 2.3%; a flow rate of 1 μL/min; $N = 3$). The microdialysis probes were bilaterally inserted through the guide cannulas into the prefrontal cortex (FCx) and nucleus accumbens (NAcc) 12 h before the experiments. Stereotaxic coordinates for the probes were as follows: FCx, AP +3.7 mm relative to the bregma, ML ± 0.7 mm relative to the midline, and DV 2.5–5.0 mm relative to the skull surface; NAcc, AP +1.2 mm relative to the bregma, ML ± 1.4 mm relative to the midline, and DV 6.5–8.0 mm relative to the skull surface. Thus, dialysates in the NAcc were comprised of both the core and shell. After probe insertion, rats were placed in a chamber that allowed animals to move freely in a microdialysis setting (Raturn® system, Bioanalytical System Inc., IN, USA). The dialysis probe was perfused overnight with artificial cerebrospinal fluid (aCSF) consisting of 140 mM NaCl, 3.0 mM KCl, 1.5 mM $CaCl_2$, 1.0 mM $MgCl_2$, 0.25 mM NaH_2PO_4, and 1.0 mM Na_2HPO_4. The aCSF was pumped at a rate of 1.0 μL/min. The next day, experiments started with four basal collections followed by eight post-treatment samples at 15 min intervals. Samples were stored at −80 °C prior to neurochemical analysis. DA was separated on a reverse-phase column (Eicompak, CA5 ODS; 2.1 mm diameter × 150 mm; Eicom). The mobile phase for the separation was 0.1 M phosphate buffer consisting of 50 mg/L EDTA, 900 mg/L sodium octanesulphonate and 10 mL/L methanol, pH 6. The measurement was conducted with an electrochemical detector (HTEC-500; Eicom, Japan). The detection limit at a signal to noise ratio of 3:1 was 0.1 pg/sample. The amount of DA in samples was calculated by comparison with the external DA standard. Data were normalized as percent (%) changes of the baseline values.

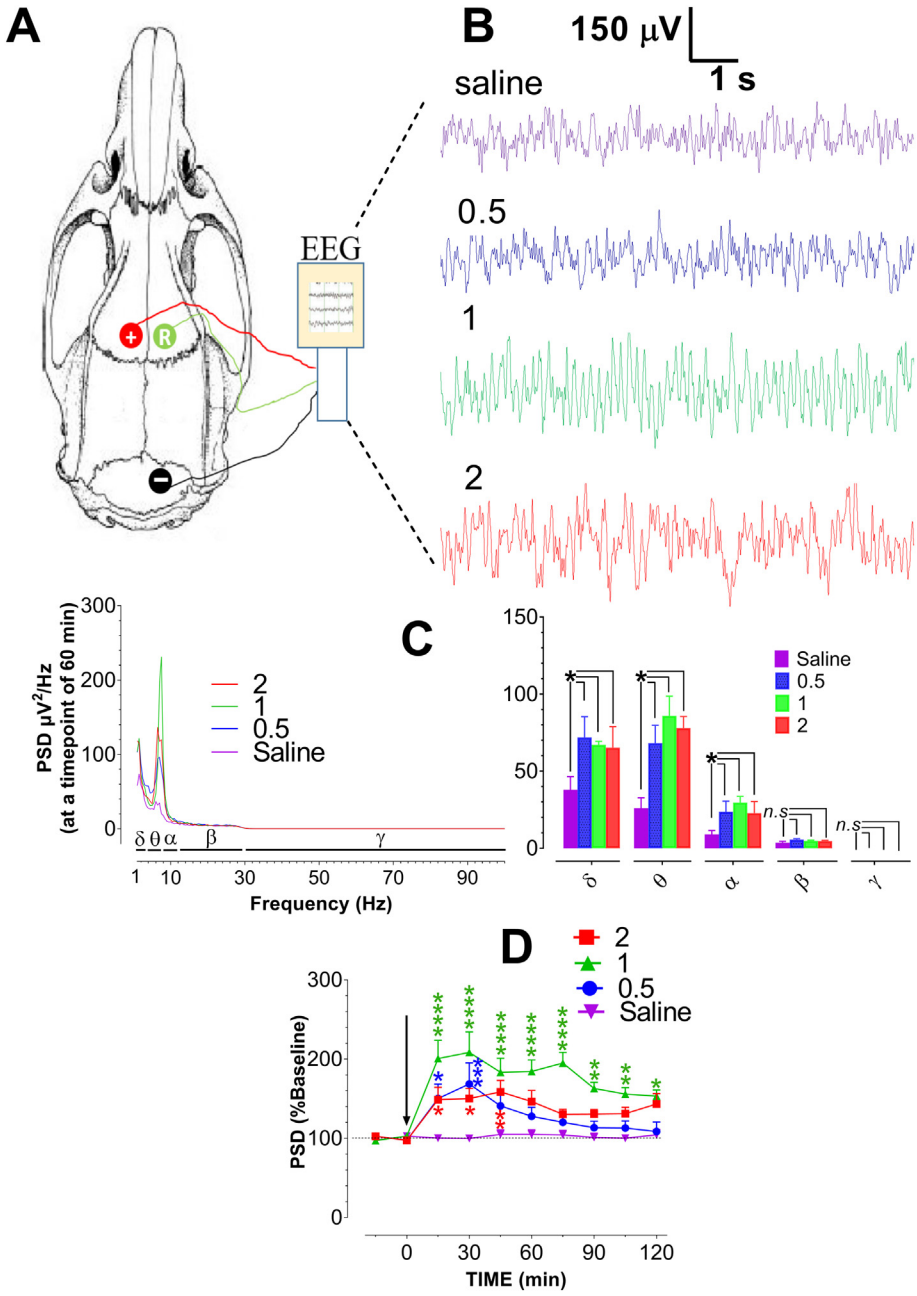

Fig. 1. EEG activity in response to MDPV administration.

A, A schematic diagram of the electrode placements on a rat scalp.

B, Examples of EEG traces representing 10-s activity 60 min after saline, 0.5 mg/kg, 1 mg/kg, or 2 mg/kg MDPV (i.p.). Horizontal scale bar: 1 s; vertical scale bar: 150 μV.

C, The relationship between EEG amplitudes and frequency (1–100 Hz) revealed by a power spectral density (PSD) analysis. PSD is expressed as mean ± SEM (μV^2/Hz; $N = 6$). Left panel: Data represent PSD levels across 1–100 Hz 60 min after saline, 0.5 mg/kg, 1 mg/kg, or 2 mg/kg MDPV (i.p.). Right panel: Compared to saline, all three doses significantly increased PSD on δ-, θ-, and α-oscillations, but not β- or γ-oscillations. *$P < .05$ vs saline, unpaired Student's *t*-test.

D, A time course of changes in PSD levels at frequency of 1–12 Hz. Data are normalized to percentage (%) of basal PSD (each group N = 6). Basal PSD (μV^2/Hz): saline, 12.32 ± 2.12; 0.5 mg/kg, 13.7 ± 2.15; 1 mg/kg, 11.95 ± 1.83; and 2 mg/kg, 12.98 ± 2.58. *P < .05, **$P < .01$, and ***$P < .001$ vs. saline, repeated measures ANOVA followed by *post-hoc* Scheffe test.

Upon completion of microdialysis, animals were deeply anesthetized with xylazine (6 mg/kg, i.p.) in combination of ketamine (100 mg/kg, i.p.). Probe inlets were perfused with 2% fast green for 5 min. Next, brain was removed, frozen at −20 °C and sliced with a blade. Probe placements were verified with viewing green tracks in comparison with the FCx and NAcc sections published in the Rat Brain Atlas (Paxinos and Watson, 1998).

2.5. Statistical analysis

All data are expressed as mean (± standard error of the mean). Two-way repeated measures ANOVA and Student's *t*-test were used to determine statistical differences between treatments at a specific sampling time. The significant differences were set at 0.05.

3. Results

3.1. Effects of MDPV

Fig. 1A displays positions of electrodes anchored on the rat scalp surface, outlining areas of the cortical regions where EEG signals were recorded. Fig. 1B displays samples of 10-s raw EEG waves recorded 60 min after saline, 0.5 mg/kg, 1 mg/kg, or 2 mg/kg MDPV administration. MDPV caused a dose-dependent increase in EEG amplitudes with a maximal effect at 1 mg/kg. Next, those 10-s raw traces at a time period of 60 min were transformed into power spectral densities (PSD; μV^2/Hz) plotted against its frequency between 1 Hz and 100 Hz (Fig. 1C). The PSD values were high at low frequency (i.e., δ, θ, and α) and low at high frequency (β and γ). Further analysis of the frequency from 1 to 100 Hz in relationship with changes in PSD revealed that MDPV administration had an effect on PSD in a frequency-dependent manner. Specifically, δ-, θ-, and α-PSDs, but not β- or γ-PSDs, were significantly elevated. Lastly, PSDs during the entire experimental time

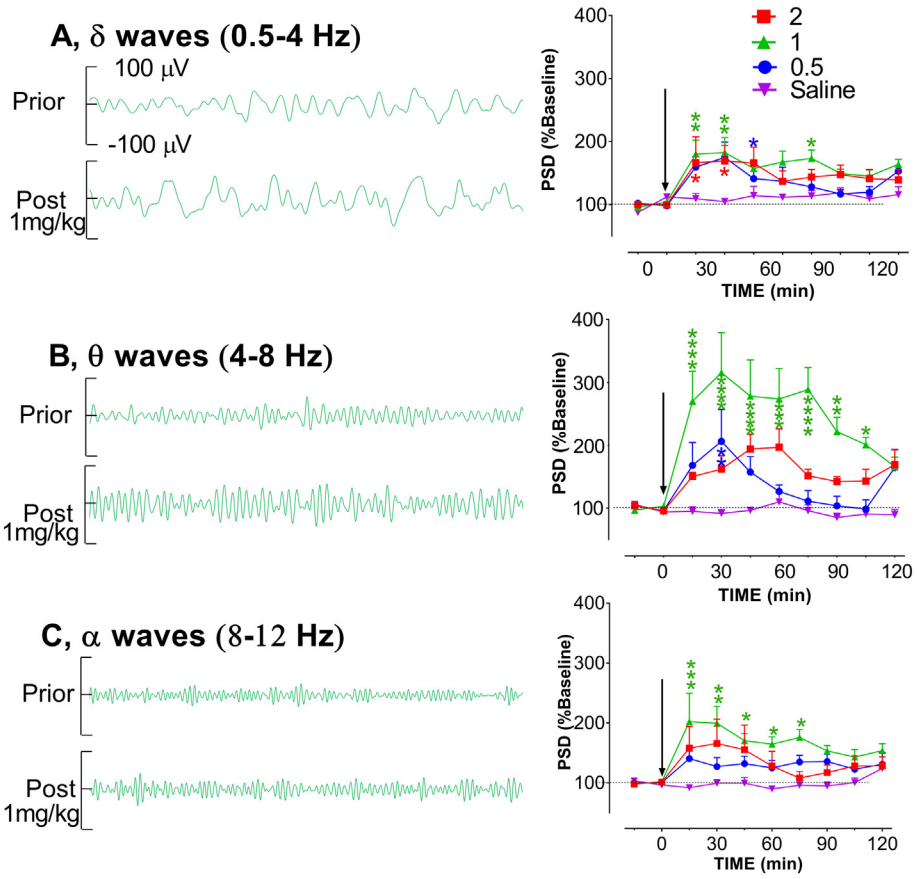

Fig. 2. Analysis of δ-, θ-, and α-oscillations in response to MDPV administration.
A, Left panel displays examples of 10-s δ-oscillations prior and 60 min after 1 mg/kg MDPV (i.p.). Right panel shows a dose-dependent increase in PSD levels of δ-oscillations.
B, Left panel displays examples of 10-s θ-oscillations prior and 60 min after 1 mg/kg MDPV (i.p.). Right panel shows a dose-dependent increase in PSD levels of θ-oscillations.
C, Left panel displays examples of 10-s α- oscillations prior and 60 min after 1 mg/kg MDPV (i.p.). Right panel shows a dose-dependent increase in PSD levels of α-oscillations.
*P < .05, **P < .01, and ***P < .001 vs. saline, repeated measures ANOVA followed by *post-hoc* Scheffe test.

period were expressed as % baseline. As shown in Fig. 1D, MDPV caused a dose-dependent increase in PSD ($F_{(3,\ 20)} = 14.105$, $P < .0001$). The maximum effect occurred at 1 mg/kg.

We next conducted a PSD analysis on δ-, θ- and α-waves cross entire experimental time. Basal PSD values (μV^2/Hz) were 28.63 ± 2.27, 16.51 ± 1.31, and 4.36 ± 0.35 for δ-, θ-, and α-waves, respectively. The left panels in Fig. 2 display 10-s waveforms prior to the drug administration (top) and 60 min after 1 mg/kg MDPV administration (bottom). Changes in PSDs during the entire experimental time were normalized to baseline values, expressed as % baseline, and displayed in the right panels. Significant increases were found in the δ ($F_{(3,\ 20)} = 3.867$, $P = .0248$), θ ($F_{(3,\ 20)} = 11.595$, $P = .0001$), and α ($F_{(3,\ 20)} = 4.696$, $P = .0122$), but not β (data not shown) or γ (data not shown).

The D_1 receptor antagonist SCH23990 (SCH) and D_2 receptor antagonist sulpiride (Pruitt et al., 1995; Banasikowski and Beninger, 2012) were used to determine receptor subtypes involved in MDPV-elicited changes in EEG activity. We noted that 0.1 mg/kg SCH alone or 100 mg/kg sulpiride alone had no effect on EEG activity (Fig. 3 left panels). In contrast, pretreatment with SCH or sulpiride reduced MDPV-elicited increases in PSD (Fig. 3 right panels). Two-way ANOVA with repeated measures revealed that those receptor antagonists exerted significant effects on MDPV-elicited increases in δ- ($F_{(2,15)} = 5.213$, $P = .0191$), θ- ($F_{(2,15)} = 13.808$, $P = .0004$), and α-synchronization ($F_{(2,15)} = 9.975$, $P = .0018$). *Post-hoc* analysis revealed that SCH pretreatment blocked all three waveforms. However, sulpiride had effects on θ- and α- but not δ-waves.

Lastly, regional specific changes in DA were determined with microdialysis in the FCx and NAcc. Fig. 4A displays placements of microdialysis probes in the FCx (left panel) and NAcc (right panel). Basal DA was 0.22 ± 0.02 pg/sample in the FCx (probe $N = 24$) and 1.11 ± 0.27 in the NAcc (probe N = 24). To compare effects of drugs, changes in DA were normalized to their pre-drug levels (% baseline). MDPV caused a dose-dependent increase in the FCx (Fig. 4B; $F_{(3,\ 20)} = 6.175$, $P = .0038$), and NAcc ($F_{(3,\ 20)} = 45.072$, $P < .0001$). Compared to the area under the curve (AUC) of 2 h collection, there is tendency that DA elevation in response to 1 mg/kg MDPV was greater in the NAcc than FCx (Fig. 4C).

3.2. Effects of MK-801 and ketamine

Compared with EEG tracers at prior drug levels, EEG amplitudes were dose-dependently increased 60 min after administration of saline (control), 0.05 mg/kg, 0.1 mg/kg and 0.5 mg/kg MK-801 (Fig. 5A). EEG amplitudes relevant to frequencies were transformed into PSD (μV^2/Hz) and displayed in Fig. 5B. Compared to the prior drug levels, MK-801 injection markedly increased the PSD values at frequencies of 1–12 Hz (Fig. 5B), but not 12–100 Hz (data not shown). Thus, the frequency filter for the rest of MK-801 EEG analysis was set at 1–12 Hz. To reveal a time course of changes in the entire experimental period, PSD data were collected every 15 min including 30 min basal activity and 120 min post-drug activity. All data were expressed as % baseline (see the details in the Method section). Injection of MK-801 caused a dose-dependent increase in the PSD (Fig. 5C; $F_{(3,\ 20)} = 9.344$, $P = .0005$). Significant increases were found at the dose as low as 0.1 mg/kg. To determine an involvement of DA, brain microdialysis was performed in the FCx and NAcc. Basal level was 0.24 ± 0.04 pg/sample (probe $N = 24$) in the FCx and 2.09 ± 0.4 pg/sample in the NAcc. We found MK-801 elicited a dose-dependent increase in the FCx (Fig. 5D; $F_{(3,\ 20)} = 10.76$, $P = .0002$). Although there was a significant increase in the NAcc ($F_{(3,\ 20)} = 5.026$, $P = .0093$), this effect occurred only at the dose of 0.5 mg/kg. Compared to the area under the curve (AUC) of 2 h collection, the DA response to MK-801 was greater in the FCx than the NAcc (Fig. 5E).

Fig. 6A shows 10-s raw EEG traces prior administration compared

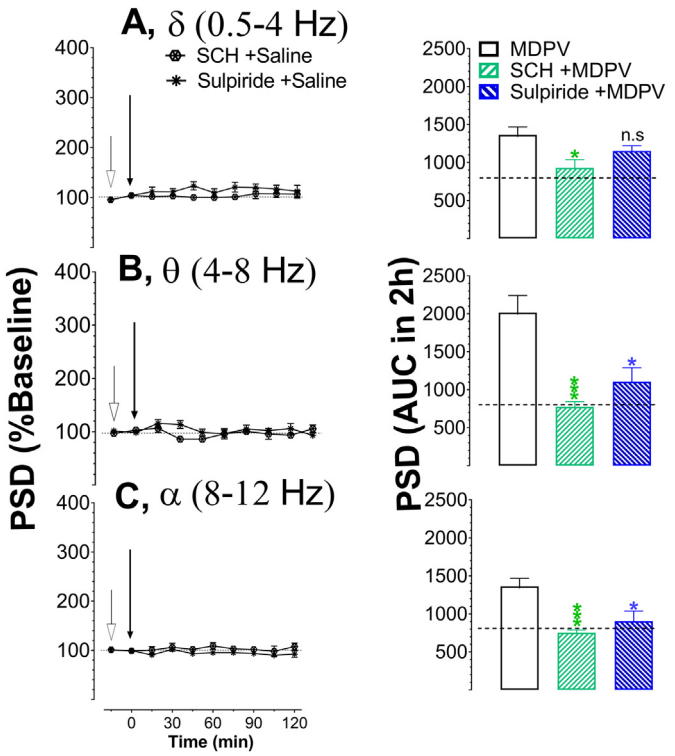

Fig. 3. Antagonistic effects of SCH23390 (SCH) and sulpiride on 1 mg/kg MDPV-induced increases in PSD levels of δ- (A), θ- (B), and α-oscillations (C). Open and solid arrows indicate times of administration with antagonists and saline, respectively. SCH (0.1 mg/kg, i.p.) alone or sulpiride (100 mg/kg, i.p.) alone had no effect on δ-, θ- or α-oscillations (left penal). $P > .05$ determined by two-way repeated measures ANOVA.

A, Pretreatment with SCH, but not sulpiride, significantly blocked the effect of MDPV on δ-oscillations.

B, Pretreatment with SCH and sulpiride significantly blocked the effect of MDPV on θ-oscillations.

C, Pretreatment with SCH and sulpiride significantly blocked the effect of MDPV on α-oscillations.

*P < .05, **P < .01, and ***P < .001 vs. MDPV examined by unpaired Student t-test.

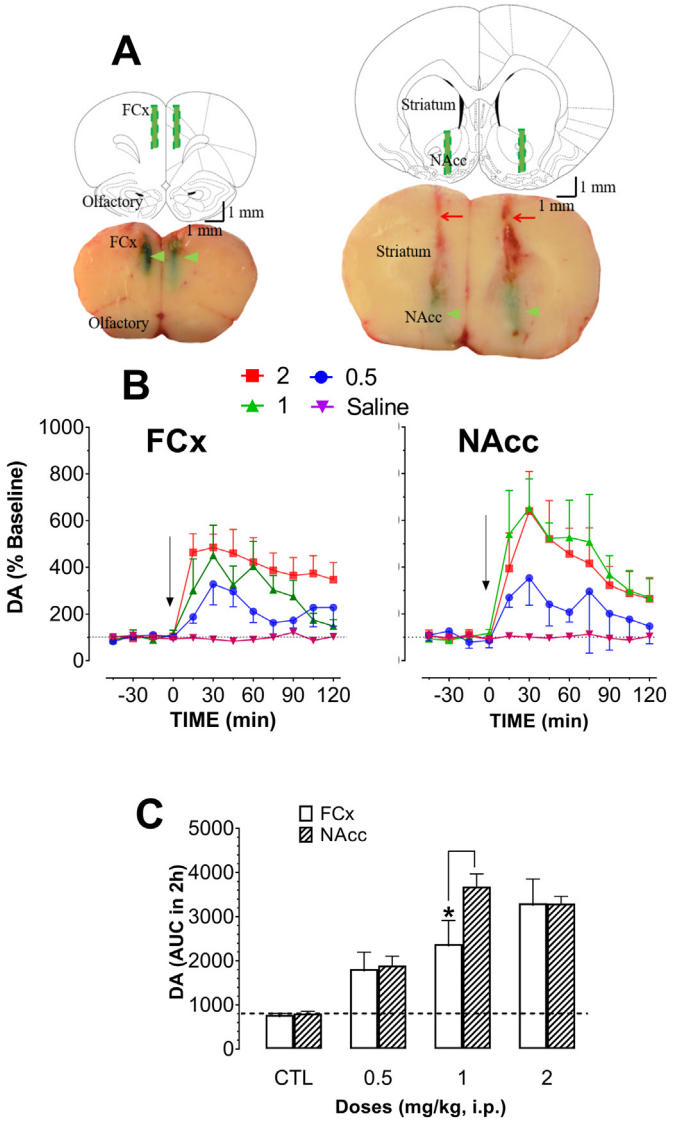

Fig. 4. Effects of MDPV on DA neurotransmissions in the prefrontal cortex (FCx) and nucleus accumbens (NAcc).

A, Schematic diagram of microdialysis probe placements in the FCx and NAcc. Green tracks (indicated by arrowheads) were traces of 2% Fast Green showing locations placed with microdialysis probes.

B, MDPV administration caused a dose-dependent increase in DA neurotransmission in both the FCx and NAcc. Two-way repeated measures ANOVA followed by *post-hoc* Scheffe test. Asterisks (*P < .05, **P < .01, ***P < .001 vs. saline) are omitted graphs for the sake of visual clarity.

C, Comparison of the effect of MDPV on DA neurotransmission in the FCx and NAcc. *P < .05 vs. NAcc, unpaired Student's t-test.

with those at other time frames after 25 mg/kg ketamine administration. The EEG amplitudes were visually increased at the early stage after drug administration. EEG amplitudes relative to their frequency bands were expressed as PSD (μV^2/Hz, for example, 60 min after drug administration, Fig. 6B). PSD data were expressed as percentage levels from respective baseline and displayed in Fig. 6C. Ketamine caused a dose-dependent increase in the PSD ($F_{(3,\ 20)} = 6.959$, $P = .0022$). Lastly, DA microdialysis was carried in the FCx and NAcc. Basal level was 0.2 ± 0.03 pg/sample (probe N = 24) in the FCx and 1.28 ± 0.27 pg/sample in the NAcc. Ketamine caused a dose-dependent increase in the FCx (Fig. 6D; $F_{(3,\ 20)} = 7.796$, $P = .0012$), but not NAcc ($F_{(3,\ 20)} = 1.692$, $P = .2009$). Compared to the area under the curve (AUC) of 2 h collection, the effect was significantly greater in the FCx than the NAcc (Fig. 6E).

The involvement of D_1 and D_2 receptors was examined with 0.1 mg/kg SCH and 100 mg/kg sulpiride, respectively. SCH or sulpiride was administered 15 min prior 1 mg/kg MK-801 or 25 mg/kg ketamine. The role of DA receptors in forming δ-, θ-, or α-bands was analyzed. First, we analyzed the role of those receptors in the δ-bands. Basal δ-PSD was 33.93 ± 2.63 μV^2/Hz and 35.48 ± 2.14 μV^2/Hz in MK-801 and ketamine groups, respectively. As shown in Fig. 7A, pretreatment with SCH (0.1 mg/kg, i.p.) or sulpiride (100 mg/kg, i.p.) blocked the effect of MK-801, but not ketamine. Next, we analyzed roles of those DA receptors in θ-wave synchronization. Basal θ-wave PSD was 16.41 ± 1.18 μV^2/Hz and 16.53 ± 1.38 μV^2/Hz in MK-801 and ketamine groups, respectively. Neither SCH nor sulpiride blocked the effect of MK-801 or ketamine (Fig. 7B). Finally, the role of DA receptors in α-synchronization was analyzed. Basal α-PSD was 4.67 ± 0.26 μV^2/Hz and 5.1 ± 0.51 μV^2/Hz in MK-801 and ketamine groups, respectively. SCH and sulpiride blocked the effect of MK-801, but not ketamine (Fig. 7C).

4. Discussion

The main findings of this comparative study are summed from three aspects. 1) All three drugs could cause an increase in cortical EEG synchrony. This increase took place at low (1–12 Hz), but not high frequencies (> 12 Hz); 2) They all caused increases in DA neurotransmission in the FCx. However, their effects on DA in the NAcc were

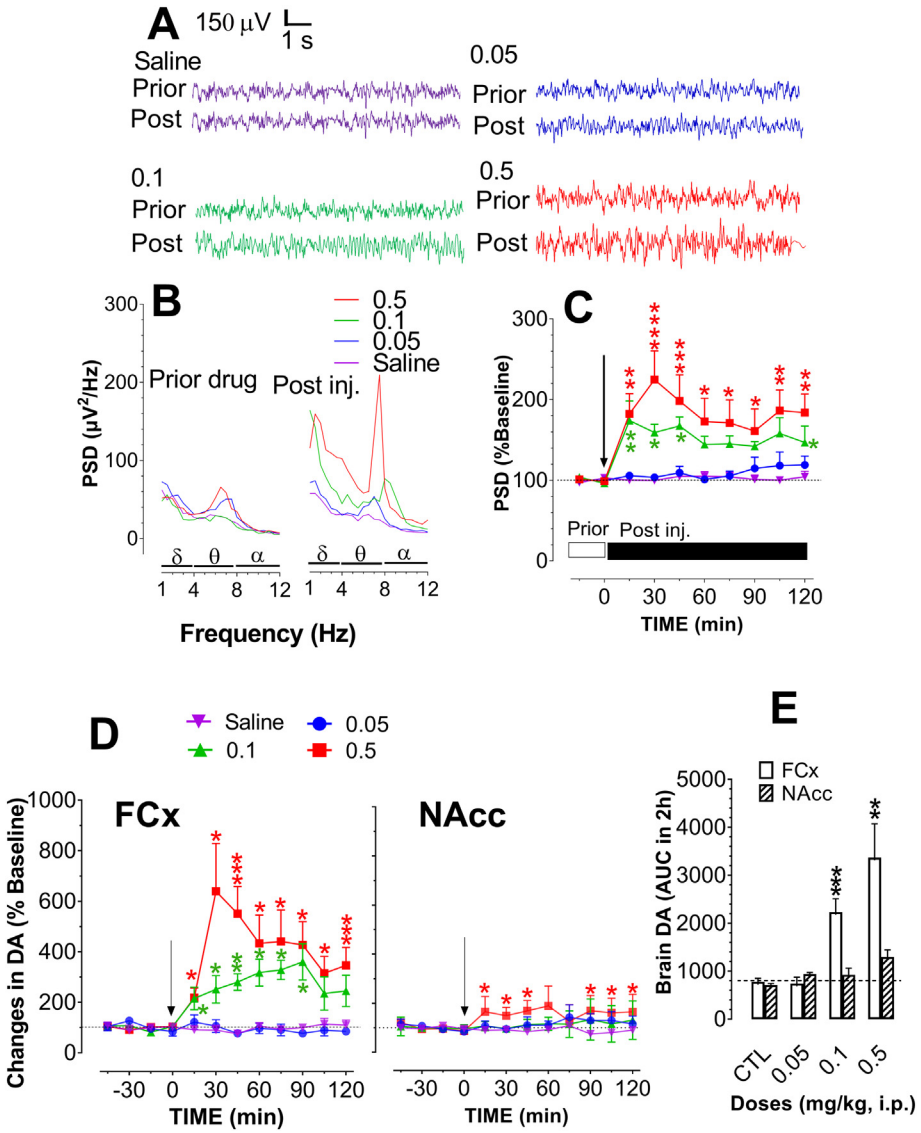

Fig. 5. Effects of MK-801.

A, EEG recordings. Example of 10-s traces representing EEG activity prior and 60 min post-injection of saline, 0.05 mg/kg, 0.1 mg/kg, or 0.5 mg/kg MK-801.

B, A dose-dependent relationship between EEG amplitudes and frequency (1–12 Hz) revealed by a power spectral density (PSD) analysis. PSD is expressed as mean ± SEM (μV^2/Hz; each group N = 6). PSD at prior-drug levels (left panel) is compared with those at 60 min after MK-801 administration (right panel).

C, A time-course of PSD (μV^2/Hz) from 1 to 12 Hz. MK-801 caused time- and dose-dependent effects on EEG synchronization. *P < .05, **P < .01, ***P < .001 vs. saline, two-way repeated measures ANOVA followed by *post-hoc* Scheffe test.

D, Effect of MK-801 on DA neurotransmission in the FCx (left panel) and NAcc (right panel). *P < .05, **P < .01, ***P < .001 vs. saline, repeated measures ANOVA followed by *post-hoc* Scheffe test.

E, Comparison of the effect of MK-801 on DA neurotransmission in the FCx and NAcc. **P < .01 and ***P < .001 vs. NAcc, unpaired Student's t-test.

strikingly different; 3) DA receptor antagonists blocked effects on EEG synchrony of MDPV and MK-801, but not ketamine. Interestingly, the D_1 receptor antagonist SCH23990 had a better efficacy than the D_2 receptor antagonist sulpiride in the antagonistic effect on the EEG synchrony. Taken together, results suggest that MDPV like MK-801 and ketamine exerts effects on the microcircuits in the cortex, causing EEG synchronization associated with hallucinations of transient psychosis. Despite utilizing DA transmission, receptor mechanisms involving MDPV-elicited increases in EEG synchronization are more similar to those for MK-801 than those for ketamine.

4.1. Methodological consideration

Brain electric currents flowing from multiple nearby neurons can be detected in vivo with several approaches, including EEG, electrocorticography, and intracerebral local field potential (LFP). The skull-based EEG is typically used in animals. In the present study, three distinct electrodes were characteristically anchored on the surface of skulls (above the dura mater), and thus EEG signals reflect spatial and temporal summations of the excitatory (EPSP) and inhibitory post-synaptic potentials (IPSP) from the apical dendrites of cortical pyramidal neurons (Kirschstein and Kohling, 2009). Given that EEG electrodes in human patients are scalp-based closely similar to this array, the data obtained in the study are translational.

In the earlier studies, EEG analysis and feature extraction were overwhelmed by superimposing EEG waves over each other with the huge variety of waveforms (Mattia and Moreton, 1986; Cerutti et al., 1987; Clementz et al., 2008), which hindered the applications in research and clinical diagnosis. Recent advantage of information technology makes it possible that EEG analysis and feature extraction can be easily accomplished with computer-assistant instruments and software, which relies on two distinct mathematical methods: fast fourier transform (FFT) and continuous wavelet transform (CWT). It seems that they are becoming increasingly important in the analysis of EEG data and the creation of new knowledge over the brain activity in live animals (Riga et al., 2014) and human patients as well (Ma et al., 2014; Fanciullacci et al., 2017) However, each method has different focus on EEG components (e.g., frequencies, potentials, and time events). In the present study the FFT was employed simply because this method can reveal the relationship between frequencies and potentials. The power spectrum density (PSD; μV^2/Hz) is one of resultants of the FFT computations, which could reduce spectral noisy by repeatedly averaging potentials with the same frequency. To minimize variations and maximize reproducibility, PSD at each time point represented an average of triplicated samples with a time-frame of 10 s. To obtain better comparison between subjects and groups, the EEG response was normalized to %

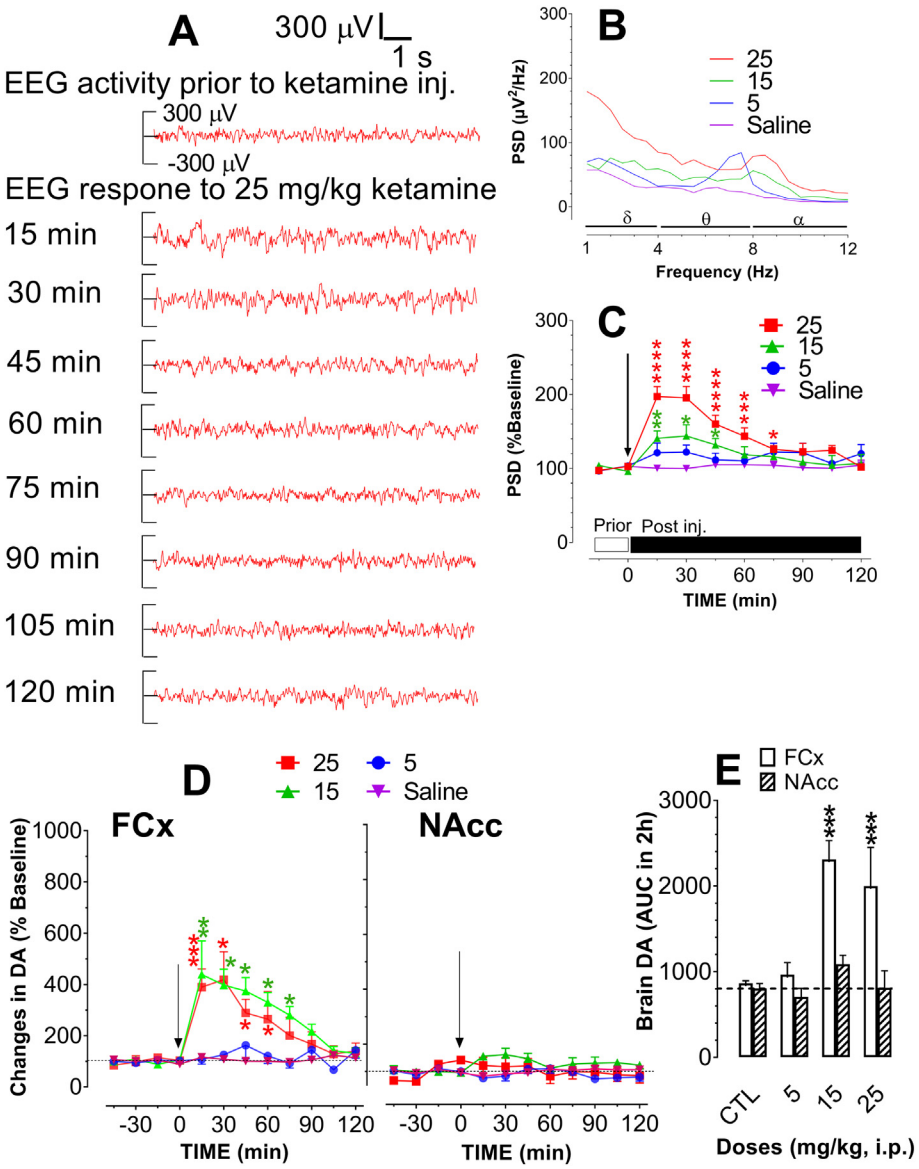

Fig. 6. Effects of ketamine.
A, EEG recordings. Example of 10-s traces representing EEG activity prior and post-injection of 25 mg/kg ketamine at the timeframe of 15–120 min.
B, A dose-dependent relationship between EEG amplitudes and frequency (1–12 Hz) revealed by a power spectral density (PSD) analysis. PSD is expressed as mean ± SEM (μV^2/Hz; each group N = 6). Data represent PSD levels 60 min after saline, 5 mg/kg, 15 mg/kg, and 25 mg/kg ketamine (i.p.).
C, A time-course of PSD (μV^2/Hz) from 1 to 12 Hz. Ketamine caused time- and dose-dependent effects on EEG synchronization. *P < .05, **P < .01, ***P < .001 vs. saline, two-way repeated measures ANOVA followed by *post-hoc* Scheffe test.
D, Effect of ketamine on DA neurotransmission in the FCx (left panel) and NAcc (right panel). *P < .05, **P < .01, ***P < .001 vs. saline, repeated measures ANOVA followed by *post-hoc* Scheffe test.
E, Comparison of the effect of ketamine on DA neurotransmission in the FCx and NAcc. ***P < .001 vs. NAcc, unpaired Student's t-test.

baseline or prior drug levels. Overall, data of the present study reflected the cortical electric activity collected from animals at the wakeful state, and normalized to prior drug level. These methodological considerations have made certain that data are highly reproducible.

4.2. EEG reflects an electric integration of activity of cortical microcircuits

Increases in EEG responses to MDPV and MK-801 were rapid and somewhat long lasting for 2 h. In contrast, the EEG response to ketamine was relatively weak. The weak and rather transit effect of ketamine was also reported in the previous animal (Cordon et al., 2015) and human works (Shaw et al., 2015). Despite those, there is no doubt that all the three drugs exert effects on increases in EEG synchrony in the rat brain. Increases in EEG synchrony have been suggested to represent a core feature of the pathophysiology of hallucinogenic drugs (Reid et al., 2006; Shaw et al., 2015), similar to those occurred in schizophrenia patients with high hallucination scores (Lee et al., 2006; Zheng et al., 2015).

The mechanisms by which MK-801 and ketamine cause increases in EEG synchronization are likely attributed to disruption of the inhibitory effects on cortical pyramidal neurons through blocking NMDA receptors in the GABAergic interneurons, consistent with the dysconnection hypothesis of schizophrenia (Cohen et al., 2015). As a result, the glutamatergic inputs to the thalamus are increased, subsequently stimulating the sensory outputs to the secondary sensory areas involving in initiating hallucination (Romon et al., 2011). EEG is a physiological extrapolation of the electric integration on the cortical pyramidal neurons and interneurons consisting of excitatory-inhibitory recurrent loops of local circuits (Szabadics et al., 2001; Kirschstein and Kohling, 2009; Gerashchenko et al., 2018). GABAergic interneurons in the cortex play a critical role in the local circuits by providing feed-forward inhibitory effects on pyramidal neurons and synchronizing neuronal activity. Some interneurons, e.g., parvalbumin-expressing inhibitory neurons, are expressed glutamatergic receptors (Jadi et al., 2016) in response to excitatory inputs (Cruikshank et al., 2007). Our data are in line with previous reports that blockade of NMDA receptors with MK-801 and ketamine caused increased synchronization of skull-based EEG (Cordon et al., 2015; Sivarao et al., 2016; Harms et al., 2018) and cortical LFP in animals (Cordon et al., 2015; Furth et al., 2017; Slovik et al., 2017).

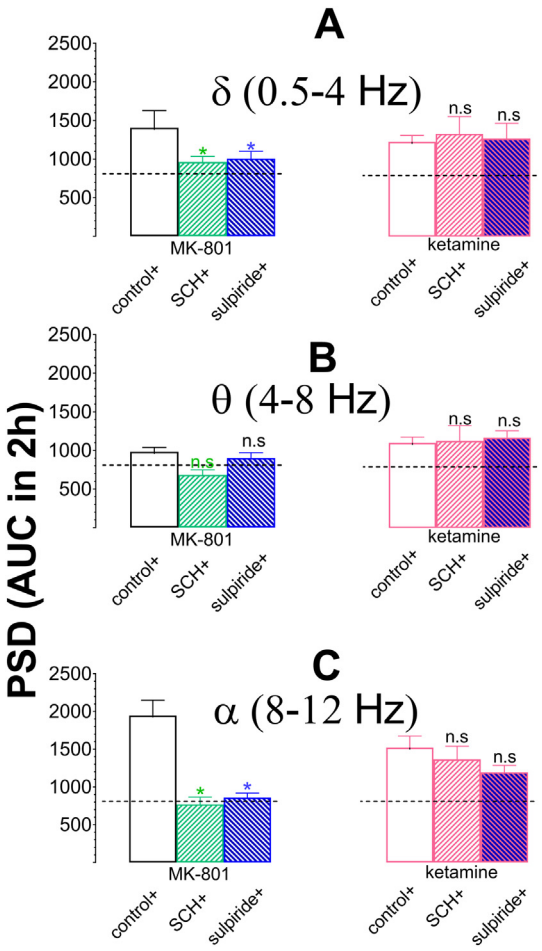

Fig. 7. Antagonistic effects of SCH23990 (SCH) and sulpiride on the hallucinogenic drug (MK-801 and ketamine) induced increases in PSD levels of δ- (A), θ- (B), and α-oscillations (C).
SCH and sulpiride blocked increases in PSD levels of δ- and α-oscillations, but not θ-oscillations caused by MK-801. Interestingly, SCH and sulpiride had no any effect on ketamine-induced changes in those oscillations. *P < .05 vs. MK-801 alone, ANOVA followed by unpaired Student's t-test.

4.3. DA elevation in the FCx, but unlikely the NAcc, involved in the EEG synchronization associated with transient psychosis

One of the objectives of the present study was to determine whether there were differences in DA elevation between the cortical and subcortical areas (e.g., NAcc) following hallucinogenic drugs. The rationale for this set of experiments was based on positron emission tomography (PET) evidence demonstrating that there was hyperdopamine in the subcortical nuclei (e.g., striatum and NAcc) and hypodopamine in the cortex of schizophrenia patients (Breier et al., 1997; Abi-Dargham et al., 1998; Thompson et al., 2013). We found that the basal DA efflux was 5–9 times greater in the NAcc than FCx, consistent with the previous microdialysis work (Moghaddam and Bunney, 1989; Pehek, 1999; Mazei et al., 2002; Carboni et al., 2006; Jedema et al., 2014). The higher basal efflux may be associated with the physiology in nature that the NAcc in contrast to the cortex has higher DA synthesis, more fibers, and greater transporter density (Sesack et al., 1998). Given differential densities in DA transporters, it is reasonable to observe that MDPV-elicited elevation in DA would be greater in the NAcc than the FCx. Increased DA (also known as hyperdopamine) in the NAcc would activate D_2 receptors, which is thought to be responsible for the hallucinatory symptoms in patients with schizophrenia (Thompson et al., 2013; Kubota et al., 2017) and the animal model of schizophrenia (Watanabe et al., 1998; Perez and Lodge, 2012; Nielsen et al., 2017). However, as discussed further below, the role of D_2 receptors was relatively weak, compared to D_1 receptors. With this regard, we suggest that the hyperdopamine hypothesis in the NAcc is unlikely the mechanisms responsible for hallucinations in the excited delirium syndrome.

We found that effects of MK-801 and ketamine were mainly in the FCx but not the NAcc, consistent with the previous reports with the noncompetitive NMDA antagonists (Schmidt and Fadayel, 1996; Lindefors et al., 1997; Kretschmer and Fink, 1999; Kuroki et al., 1999; Hatip-Al-Khatib et al., 2001; Kokkinou et al., 2018). The results were also consistent with the hypothesis that the hallucinogenic effects of MK-801 and ketamine are mainly through cortical microcircuits as discussed earlier (Cohen et al., 2015). The increase in DA can be ascribed as an intermediate result of antagonizing non-competitive NMDA receptors in the microcircuits. Ketamine, but not MK-801, was also found to have a property of inhibiting DA transporters (Nishimura and Sato, 1999; Crosby et al., 2002). However, recent studies demonstrated that a low concentration of ketamine had no affinity to the DA transporters (Can et al., 2016). Nevertheless, the results implicate that elevation in cortical DA was the common mechanisms between the two hallucinogenic drugs and MDPV. In schizophrenia patients, cortical DA transmission is poor due to cortical atrophy (Cohen et al., 2015; Arnsten et al., 2017). This “DA deficits” hypothesis is apparently not applicable to the effects of either MK-801, ketamine or MDPV. On the contrary, there was excessive DA in the cortex. Excessive DA would likely activate D_1 and D_2 receptors in the microcircuits. Therefore, we argue that increases in cortical DA would be likely attributed to hallucination. However, further investigation is certainly warranted.

4.4. Effects of MDPV on EEG attributed to D_1 receptors and to a small extent D_2 receptors

In mammalians, DA exerts its effect via GPCRs belonging to two major subclasses of receptors: the D_1 class (D_1 and D_5) and the D_2 class (D_2, D_3 and D_4). The classification is based on their ability to activate the stimulatory G protein $G_{\alpha s/olf}$ and inhibitory G protein $G_{\alpha i/o}$ signaling pathway, respectively. Although both the D_1 and D_2 receptors are found to express in the interneurons (Santana and Artigas, 2017) and pyramidal neurons (Mocci et al., 2014; Clarkson et al., 2017), studies suggest that two receptors are not colocalized at the same neurons but coactivated in functional interconnected microcircuits (Xu and Yao, 2010). It appears that interneurons preferentially recruit D_2 receptors while pyramidal neurons are functionally regulated by D_1 receptors (Tseng and O'Donnell, 2007; Yuen and Yan, 2009; Xu and Yao, 2010). The mechanisms by which MDPV caused EEG synchronization are likely ascribed to activation of D_1 and D_2 receptors in the pyramidal neurons and interneurons, respectively. As a result, the excitatory signaling from the pyramidal neurons would be enhanced, which may explain our findings of the increased synchronization in response to MDPV.

We found that SCH23990 was relatively more prominent than sulpiride in the antagonistic effects on EEG synchronization caused by MDPV and MK-801, suggesting that drug-elicited hallucination is preferential through D_1 receptors. Most antipsychotics currently available to patients exhibit more selective on D_2 than D_1 receptors (Kusumi et al., 2015) and are developed almost exclusively for schizophrenia patients. However, schizophrenia is an idiopathic disease. Although the difference between idiopathic and iatrogenic hallucinations is unknown, accumulative evidence suggests that drug-elicited hallucination was well response to D_1 receptor antagonists (O'Neill and Shaw, 1999; Hall et al., 2009; Xu and Kang, 2016) but only to small extent response to D_2 receptor antagonists (Ushijima et al., 1995; Le et al., 1997), consistent with our observation. Interestingly, neither SCH23990 nor sulpiride affected ketamine-elicited increases in EEG synchronization, implicating involvement of D_3, D_4 or D_5 receptors. Alternatively, there

are non-DA mechanisms responsible for the effect of ketamine. 5-HT_{2A} and adrenergic α_1 receptors are non-DA mechanisms potentially involving idiopathic hallucinations in schizophrenia (Romon et al., 2014; Kusumi et al., 2015), which should be examined in the future studies.

Previous studies suggest that cortical pyramidal glutamatergic neurons are necessary for the generation of low rhythms (e.g., δ, θ, or α), while GABAergic interneurons generate high oscillations (γ) for local synchrony of cortical microcircuits (Fellin et al., 2009; Veit et al., 2017; Niethard et al., 2018). In the present study, findings that the EEG synchrony occurred on the low rhythms (< 12 Hz; δ, θ, and α), but not the fast rhythms (> 12 Hz; β- and γ-oscillations) suggest that the EEG synchrony took place mainly on pyramidal glutamatergic neurons. It is consistent with observation that scalp-based EEG in human mainly allows analysis of low frequency ascribed to activity of glutamatergic neurons, but less sensitive to the high frequency relevant to GABAergic oscillation (Burnos et al., 2016; Waldert, 2016). However, abnormal changes in γ oscillations are believed to contribute impairments in cognitive and psychosocial functions in both the animal model of schizophrenic disorder (Hiyoshi et al., 2014; Furth et al., 2017), and patients with schizophrenia (Light et al., 2017; Grent-'t-Jong et al., 2018). Thus, the lack of effects on high frequency oscillations obtained in this study should be carefully interpreted and different electric approaches are needed before reaching a conclusion.

4.5. Conclusion

In the present studies, we have compared effects of MDPV with the hallucinogenic drugs MK-801 and ketamine through analyzing EEG synchronization, DA, D_1 and D_2 receptors in the rat brain. We found that MDPV similar to MK-801 and ketamine elicited an increase in EEG synchronization. MDPV also shared some similarities with MK-801 and ketamine at DA elevation in the FCx, but not the NAcc. This suggests that the FCx DA may mediate microcircuits in regulating EEG synchrony although possible involvement of NAcc DA in MDPV-elicited hallucination could not be excluded. Utilizing SCH23990 and sulpiride, we revealed involvement of D_1 and D_2 receptors in the hallucinogenic response to MDPV and MK-801, but not ketamine. We noted effects of MDPV similar to other psychostimulants (O'Neill and Shaw, 1999; Hall et al., 2009; Xu and Kang, 2016) were more sensitive to D_1 than D_2 receptor antagonists. Thus, an exploration of the therapeutic value of D_1 receptors is greatly warranted, particularly for treating drug-elicited hallucination.

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Ethics approval

Animal handling and tests were approved by the Florida Atlantic University and Ross University School of Veterinary Medicine Instructional Animal Care and Use Committee (IACUC).

Consent for publication

Not applicable.

Competing interests

None.

Availability of data and materials

The authors declare that data supporting the findings of this study are available within the article.

References

Romon, T., Planas, A.M., Adell, A., 2014. Blockade of MK-801-induced heat shock protein 72/73 in rat brain by antipsychotic and monoaminergic agents targeting D2, 5-HT1A, 5-HT2A and alpha1-adrenergic receptors. CNS & Neurol. Disord. Drug Targets 13, 104–111.

Abi-Dargham, A., Gil, R., Krystal, J., Baldwin, R.M., Seibyl, J.P., Bowers, M., van Dyck, C.H., Charney, D.S., Innis, R.B., Laruelle, M., 1998. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am. J. Psychiatry 155, 761–767.

Arnsten, A.F., Girgis, R.R., Gray, D.L., Mailman, R.B., 2017. Novel dopamine therapeutics for cognitive deficits in schizophrenia. Biol. Psychiatry 81, 67–77.

Banasikowski, T.J., Beninger, R.J., 2012. Haloperidol conditioned catalepsy in rats: a possible role for D1-like receptors. Int. J. Neuropsychopharmacol. 15, 1525–1534.

Baumann, M.H., Bukhari, M.O., Lehner, K.R., Anizan, S., Rice, K.C., Concheiro, M., Huestis, M.A., 2017. Neuropharmacology of 3,4-methylenedioxypyrovalerone (MDPV), its metabolites, and related analogs. Curr. Top. Behav. Neurosci. 32, 93–117.

Breier, A., Su, T.P., Saunders, R., Carson, R.E., Kolachana, B.S., de Bartolomeis, A., Weinberger, D.R., Weisenfeld, N., Malhotra, A.K., Eckelman, W.C., Pickar, D., 1997. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc. Natl. Acad. Sci. U. S. A. 94, 2569–2574.

Burnos, S., Fedele, T., Schmid, O., Krayenbuhl, N., Sarnthein, J., 2016. Detectability of the somatosensory evoked high frequency oscillation (HFO) co-recorded by scalp EEG and ECoG under propofol. NeuroImage Clin. 10, 318–325.

Can, A., Zanos, P., Moaddel, R., Kang, H.J., Dossou, K.S., Wainer, I.W., Cheer, J.F., Frost, D.O., Huang, X.P., Gould, T.D., 2016. Effects of ketamine and ketamine metabolites on evoked striatal dopamine release, dopamine receptors, and monoamine transporters. J. Pharmacol. Exp. Ther. 359, 159–170.

Carboni, E., Silvagni, A., Vacca, C., Di Chiara, G., 2006. Cumulative effect of norepinephrine and dopamine carrier blockade on extracellular dopamine increase in the nucleus accumbens shell, bed nucleus of stria terminalis and prefrontal cortex. J. Neurochem. 96, 473–481.

Cerutti, S., Baselli, G., Liberati, D., Pavesi, G., 1987. Single sweep analysis of visual evoked potentials through a model of parametric identification. Biol. Cybern. 56, 111–120.

Clarkson, R.L., Liptak, A.T., Gee, S.M., Sohal, V.S., Bender, K.J., 2017. D3 Receptors Regulate Excitability in a Unique Class of Prefrontal Pyramidal Cells. J. Neurosci. 37, 5846–5860.

Clementz, B.A., Wang, J., Keil, A., 2008. Normal electrocortical facilitation but abnormal target identification during visual sustained attention in schizophrenia. J. Neurosci. 28, 13411–13418.

Cohen, S.M., Tsien, R.W., Goff, D.C., Halassa, M.M., 2015. The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. Schizophr. Res. 167, 98–107.

Cordon, I., Nicolas, M.J., Arrieta, S., Lopetegui, E., Lopez-Azcarate, J., Alegre, M., Artieda, J., Valencia, M., 2015. Coupling in the cortico-basal ganglia circuit is aberrant in the ketamine model of schizophrenia. European neuropsychopharmacology 25, 1375–1387.

Crosby, M.J., Hanson, J.E., Fleckenstein, A.E., Hanson, G.R., 2002. Phencyclidine increases vesicular dopamine uptake. Eur. J. Pharmacol. 438, 75–78.

Cruikshank, S.J., Lewis, T.J., Connors, B.W., 2007. Synaptic basis for intense thalamocortical activation of feedforward inhibitory cells in neocortex. Nat. Neurosci. 10, 462–468.

Desharnais, B., Daze, Y., Huppertz, L.M., Mireault, P., Skinner, C.D., 2017. A case of fatal idiosyncratic reaction to the designer drug 3,4-methylenedioxypyrovalerone (MDPV) and review of the literature. Forensic Sci. Med. Pathol. 13, 350–354.

Diestelmann, M., Zangl, A., Herrle, I., Koch, E., Graw, M., Paul, L.D., 2018. MDPV in forensic routine cases: Psychotic and aggressive behavior in relation to plasma concentrations. Forensic Sci. Int. 283, 72–84.

Fanciullacci, C., Bertolucci, F., Lamola, G., Panarese, A., Artoni, F., Micera, S., Rossi, B., Chisari, C., 2017. Delta power is higher and more symmetrical in ischemic stroke patients with cortical involvement. Front. Hum. Neurosci. 11, 385.

Fellin, T., Halassa, M.M., Terunuma, M., Succol, F., Takano, H., Frank, M., Moss, S.J., Haydon, P.G., 2009. Endogenous nonneuronal modulators of synaptic transmission control cortical slow oscillations in vivo. Proc. Natl. Acad. Sci. U. S. A. 106, 15037–15042.

Furth, K.E., McCoy, A.J., Dodge, C., Walters, J.R., Buonanno, A., Delaville, C., 2017. Neuronal correlates of ketamine and walking induced gamma oscillations in the medial prefrontal cortex and mediodorsal thalamus. PLoS One 12, e0186732.

Gerashchenko, D., Schmidt, M.A., Zielinski, M.R., Moore, M.E., Wisor, J.P., 2018. Sleep State Dependence of Optogenetically evoked responses in Neuronal Nitric Oxide

Synthase-positive Cells of the Cerebral Cortex. Neuroscience 379, 189–201.
Grent-'t-Jong, T., Rivolta, D., Gross, J., Gajwani, R., Lawrie, S.M., Schwannauer, M., Heidegger, T., Wibral, M., Singer, W., Sauer, A., Scheller, B., Uhlhaas, P.J., 2018. Acute ketamine dysregulates task-related gamma-band oscillations in thalamo-cortical circuits in schizophrenia. Brain 141, 2511–2526.
Hall, D.A., Powers, J.P., Gulley, J.M., 2009. Blockade of D1 dopamine receptors in the medial prefrontal cortex attenuates amphetamine- and methamphetamine-induced locomotor activity in the rat. Brain Res. 1300, 51–57.
Harms, L., Fulham, W.R., Todd, J., Meehan, C., Schall, U., Hodgson, D.M., Michie, P.T., 2018. Late deviance detection in rats is reduced, while early deviance detection is augmented by the NMDA receptor antagonist MK-801. Schizophr. Res. 191, 43–50.
Hatip-Al-Khatib, I., Mishima, K., Iwasaki, K., Fujiwara, M., 2001. Microdialysates of amines and metabolites from core nucleus accumbens of freely moving rats are altered by dizocilpine. Brain Res. 902, 108–118.
Hiyoshi, T., Kambe, D., Karasawa, J., Chaki, S., 2014. Involvement of glutamatergic and GABAergic transmission in MK-801-increased gamma band oscillation power in rat cortical electroencephalograms. Neuroscience 280, 262–274.
Jadi, M.P., Behrens, M.M., Sejnowski, T.J., 2016. Abnormal Gamma Oscillations in N-Methyl-D-Aspartate Receptor Hypofunction Models of Schizophrenia. Biol. Psychiatry 79, 716–726.
Jedema, H.P., Narendran, R., Bradberry, C.W., 2014. Amphetamine-induced release of dopamine in primate prefrontal cortex and striatum: striking differences in magnitude and timecourse. J. Neurochem. 130, 490–497.
John, M.E., Thomas-Rozea, C., Hahn, D., 2017. Bath salts abuse leading to new-onset psychosis and potential for violence. Clin. Schizophrenia Related Psychoses 11, 120–124.
Karch, S.B., 2015. Cathinone neurotoxicity ("the 3Ms"). Curr. Neuropharmacol. 13, 21–25.
Kirschstein, T., Kohling, R., 2009. What is the source of the EEG? Clin. EEG Neurosci. 40, 146–149.
Kokkinou, M., Ashok, A.H., Howes, O.D., 2018. The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. Mol. Psychiatry 23, 59–69.
Kretschmer, B.D., Fink, S., 1999. Spatial learning deficit after NMDA receptor blockade and state-dependency. Behav. Pharmacol. 10, 423–428.
Kubota, M., Nagashima, T., Takano, H., Kodaka, F., Fujiwara, H., Takahata, K., Moriguchi, S., Kimura, Y., Higuchi, M., Okubo, Y., Takahashi, H., Ito, H., Suhara, T., 2017. Affinity States of Striatal Dopamine D2 Receptors in Antipsychotic-Free patients with Schizophrenia. Int. J. Neuropsychopharmacol. 20, 928–935.
Kuroki, T., Kawahara, T., Yonezawa, Y., Tashiro, N., 1999. Effects of the serotonin2A/2C receptor agonist and antagonist on phencyclidine-induced dopamine release in rat medial prefrontal cortex. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 23, 1259–1275.
Kusumi, I., Boku, S., Takahashi, Y., 2015. Psychopharmacology of atypical antipsychotic drugs: from the receptor binding profile to neuroprotection and neurogenesis. Psychiatry Clin. Neurosci. 69, 243–258.
Le, A.D., Tomkins, D., Higgins, G., Quan, B., Sellers, E.M., 1997. Effects of 5-HT3, D1 and D2 receptor antagonists on ethanol- and cocaine-induced locomotion. Pharmacol. Biochem. Behav. 57, 325–332.
Lee, S.H., Wynn, J.K., Green, M.F., Kim, H., Lee, K.J., Nam, M., Park, J.K., Chung, Y.C., 2006. Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations. Schizophr. Res. 83, 111–119.
Light, G.A., Zhang, W., Joshi, Y.B., Bhakta, S., Talledo, J.A., Swerdlow, N.R., 2017. Single-Dose Memantine Improves Cortical Oscillatory Response Dynamics in patients with Schizophrenia. Neuropsychopharmacology 42, 2633–2639.
Lindefors, N., Barati, S., O'Connor, W.T., 1997. Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res. 759, 205–212.
Ma, J., Svetnik, V., Snyder, E., Lines, C., Roth, T., Herring, W.J., 2014. Electroencephalographic power spectral density profile of the orexin receptor antagonist suvorexant in patients with primary insomnia and healthy subjects. Sleep 37, 1609–1619.
Mangewala, V., Sarwar, S.R., Shah, K., Singh, T., 2013. Bath salts-induced psychosis: a case report. Innovations Clin. Neurosci. 10, 10–11.
Mattia, A., Moreton, J.E., 1986. Electroencephalographic (EEG), EEG power spectra, and behavioral correlates in rats given phencyclidine. Neuropharmacology 25, 763–769.
Mazei, M.S., Pluto, C.P., Kirkbride, B., Pehek, E.A., 2002. Effects of catecholamine uptake blockers in the caudate-putamen and subregions of the medial prefrontal cortex of the rat. Brain Res. 936, 58–67.
McKetin, R., Gardner, J., Baker, A.L., Dawe, S., Ali, R., Voce, A., Leach, L.S., Lubman, D.I., 2016. Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users. Psychiatry Res. 238, 166–171.
Mocci, G., Jimenez-Sanchez, L., Adell, A., Cortes, R., Artigas, F., 2014. Expression of 5-HT2A receptors in prefrontal cortex pyramidal neurons projecting to nucleus accumbens. Potential relevance for atypical antipsychotic action. Neuropharmacology 79, 49–58.
Moghaddam, B., Bunney, B.S., 1989. Differential effect of cocaine on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens: comparison to amphetamine. Synapse 4, 156–161.
Mori, T., Iwase, Y., Murata, A., Iwata, N., Suzuki, T., 2016. Brain site- and transmitter-dependent actions of methamphetamine, morphine and antipsychotics. Behav. Brain Res. 306, 64–70.
Nielsen, J., Fejgin, K., Sotty, F., Nielsen, V., Mork, A., Christoffersen, C.T., Yavich, L., Lauridsen, J.B., Clausen, D., Larsen, P.H., Egebjerg, J., Werge, T.M., Kallunki, P., Christensen, K.V., Didriksen, M., 2017. A mouse model of the schizophrenia-associated 1q21.1 microdeletion syndrome exhibits altered mesolimbic dopamine transmission. Transl. Psychiatry 7, 1261.
Niethard, N., Ngo, H.V., Ehrlich, I., Born, J., 2018. Cortical circuit activity underlying sleep slow oscillations and spindles. Proc. Natl. Acad. Sci. U. S. A. 115, E9220–E9229.
Nishimura, M., Sato, K., 1999. Ketamine stereoselectively inhibits rat dopamine transporter. Neurosci. Lett. 274, 131–134.
Okimura, T., Tanaka, S., Maeda, T., Kato, M., Mimura, M., 2015. Simulation of the capacity and precision of working memory in the hypodopaminergic state: Relevance to schizophrenia. Neuroscience 295, 80–89.
O'Neill, M.F., Shaw, G., 1999. Comparison of dopamine receptor antagonists on hyperlocomotion induced by cocaine, amphetamine, MK-801 and the dopamine D1 agonist C-APB in mice. Psychopharmacology 145, 237–250.
Paxinos, G., Watson, C., 1998. The rat brain in stereotaxic coordniates.
Pehek, E.A., 1999. Comparison of effects of haloperidol administration on amphetamine-stimulated dopamine release in the rat medial prefrontal cortex and dorsal striatum. J. Pharmacol. Exp. Ther. 289, 14–23.
Penders, T.M., Gestring, R.E., Vilensky, D.A., 2012. Excited delirium following use of synthetic cathinones (bath salts). Gen. Hosp. Psychiatry 34, 647–650.
Perez, S.M., Lodge, D.J., 2012. Aberrant dopamine D2-like receptor function in a rodent model of schizophrenia. J. Pharmacol. Exp. Ther. 343, 288–295.
Pinault, D., 2008. N-methyl d-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant gamma oscillations in the rat neocortex. Biol. Psychiatry 63, 730–735.
Pruitt, D.L., Bolanos, C.A., McDougall, S.A., 1995. Effects of dopamine D1 and D2 receptor antagonists on cocaine-induced place preference conditioning in preweanling rats. Eur. J. Pharmacol. 283, 125–131.
Reid, M.S., Flammino, F., Howard, B., Nilsen, D., Prichep, L.S., 2006. Topographic imaging of quantitative EEG in response to smoked cocaine self-administration in humans. Neuropsychopharmacology 31, 872–884.
Riga, M.S., Soria, G., Tudela, R., Artigas, F., Celada, P., 2014. The natural hallucinogen 5-MeO-DMT, component of Ayahuasca, disrupts cortical function in rats: reversal by antipsychotic drugs. Int. J. Neuropsychopharmacol. 17, 1269–1282.
Romon, T., Mengod, G., Adell, A., 2011. Expression of parvalbumin and glutamic acid decarboxylase-67 after acute administration of MK-801. Implications for the NMDA hypofunction model of schizophrenia. Psychopharmacology 217, 231–238.
Ross, E.A., Reisfield, G.M., Watson, M.C., Chronister, C.W., Goldberger, B.A., 2012. Psychoactive "bath salts" intoxication with methylenedioxypyrovalerone. Am. J. Med. 125, 854–858.
Santana, N., Artigas, F., 2017. Laminar and cellular distribution of monoamine receptors in rat medial prefrontal cortex. Front. Neuroanat. 11, 87.
Schmidt, C.J., Fadayel, G.M., 1996. Regional effects of MK-801 on dopamine release: effects of competitive NMDA or 5-HT2A receptor blockade. J. Pharmacol. Exp. Ther. 277, 1541–1549.
Sesack, S.R., Hawrylak, V.A., Matus, C., Guido, M.A., Levey, A.I., 1998. Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. J. Neurosci. 18, 2697–2708.
Shaw, A.D., Saxena, N., Ej, L., Hall, J.E., Singh, K.D., Muthukumaraswamy, S.D., 2015. Ketamine amplifies induced gamma frequency oscillations in the human cerebral cortex. Eur. Neuropsychopharmacol. 25, 1136–1146.
Shokry, I.M., Callanan, J.J., Tao, R., 2018. Cortical dopamine is essential for the hallucinogenic effect of 3,4-methylenedioxypyrovalerone (MDPV) demonstrated by enhanced EEG activity in rats. Eur. Neuropsychopharmacol. 28 (Suppliment).
Sivarao, D.V., Chen, P., Senapati, A., Yang, Y., Fernandes, A., Benitex, Y., Whiterock, V., Li, Y.W., Ahlijanian, M.K., 2016. 40 Hz Auditory Steady-State Response is a Pharmacodynamic Biomarker for Cortical NMDA Receptors. Neuropsychopharmacology 41, 2232–2240.
Slovik, M., Rosin, B., Moshel, S., Mitelman, R., Schechtman, E., Eitan, R., Raz, A., Bergman, H., 2017. Ketamine induced converged synchronous gamma oscillations in the cortico-basal ganglia network of nonhuman primates. J. Neurophysiol. 118, 917–931.
Stevenson, R., Tuddenham, L., 2014. Novel psychoactive substance intoxication resulting in attempted murder. J. Forensic Legal Med. 25, 60–61.
Stiles, B.M., Fish, A.F., Cook, C.A., Silva, V., 2016. Bath salt-induced psychosis: nursing assessment, diagnosis, teatment, and outcomes. Perspect. Psychiatric Care 52, 68–78.
Szabadics, J., Lorincz, A., Tamas, G., 2001. Beta and gamma frequency synchronization by dendritic gabaergic synapses and gap junctions in a network of cortical interneurons. J. Neurosci. 21, 5824–5831.
Thanos, P.K., Kim, R., Delis, F., Rocco, M.J., Cho, J., Volkow, N.D., 2017. Effects of chronic methamphetamine on psychomotor and cognitive functions and dopamine signaling in the brain. Behav. Brain Res. 320, 282–290.
Thompson, J.L., Urban, N., Slifstein, M., Xu, X., Kegeles, L.S., Girgis, R.R., Beckerman, Y., Harkavy-Friedman, J.M., Gil, R., Abi-Dargham, A., 2013. Striatal dopamine release in schizophrenia comorbid with substance dependence. Mol. Psychiatry 18, 909–915.
Tseng, K.Y., O'Donnell, P., 2007. D2 dopamine receptors recruit a GABA component for their attenuation of excitatory synaptic transmission in the adult rat prefrontal cortex. Synapse 61, 843–850.
Ushijima, I., Carino, M.A., Horita, A., 1995. Involvement of D1 and D2 dopamine systems in the behavioral effects of cocaine in rats. Pharmacol. Biochem. Behav. 52, 737–741.
Veit, J., Hakim, R., Jadi, M.P., Sejnowski, T.J., Adesnik, H., 2017. Cortical gamma band synchronization through somatostatin interneurons. Nat. Neurosci. 20, 951–959.
Waldert, S., 2016. Invasive vs. non-invasive neuronal signals for brain-machine interfaces: will one prevail? Front. Neurosci. 10, 295.
Watanabe, M., Nonaka, R., Hagino, Y., Kodama, Y., 1998. Effects of prenatal methylazoxymethanol treatment on striatal dopaminergic systems in rat brain. Neurosci. Res. 30, 135–144.
Xu, S., Kang, U.G., 2016. Region-specific activation of the AMPK system by cocaine: the

role of D1 and D2 receptors. Pharmacol. Biochem. Behav. 146-147, 28–34.
Xu, T.X., Yao, W.D., 2010. D1 and D2 dopamine receptors in separate circuits cooperate to drive associative long-term potentiation in the prefrontal cortex. Proc. Natl. Acad. Sci. U. S. A. 107, 16366–16371.
Yuen, E.Y., Yan, Z., 2009. Dopamine D4 receptors regulate AMPA receptor trafficking and glutamatergic transmission in GABAergic interneurons of prefrontal cortex. J. Neurosci. 29, 550–562.
Zheng, L., Chai, H., Yu, S., Xu, Y., Chen, W., Wang, W., 2015. EEG theta power and coherence to octave illusion in first-episode paranoid schizophrenia with auditory hallucinations. Psychopathology 48, 36–46.