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ORIGINAL ARTICLE

# Prophylactic efficacy of cannabidiol and sodium nitroprusside in a ketamine model of schizophrenia: sex-dependent effects on positive-like and cognitive impairments

Daniel B.A. **Prado**,[1]* Matheus T. **Rossignoli**,[1,2]* Rafael N. **Ruggiero**,[3] José E.P. **Santos**,[4] João P. **Leite**,[1,5] Serdar M. **Dursun**,[5,6] Leman H. **Dursun**,[1,7] Antonio W. **Zuardi**,[1,5] Rafael G. **dos Santos**,[1,5] Vanessa C. **Abilio**,[5,8] João **Abrão**,[5] José A. **Crippa**,[1,5] Gleiciane G. **Avelar**,[9] Jaime E.C. **Hallak**,[1,5,6,9] Isabella C.S. **Dias**[1,5,9]

[1]*Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil.* [2]*Departamento de Ciências Biológicas, Pontifícia Universidade Católica de Minas Gerais, Poços de Caldas, MG, Brazil.* [3]*Departamento de Psicobiologia, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.* [4]*Departamento de Neurologia e Neurocirurgia, UNIFESP, São Paulo, SP, Brazil.* [5]*Instituto Nacional de Medicina Translacional, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Ribeirão Preto, SP, Brazil.* [6]*Department of Psychiatry, Neurochemical Research Unit, University of Alberta, Edmonton, AB, Canada.* [7]*Department of Clinical and Experimental Medicine, Brighton and Sussex Medical School, University of Sussex, Falmer, United Kingdom.* [8]*Departamento de Farmacologia, UNIFESP, São Paulo, SP, Brazil.* [9]*Departamento de Saúde Mental e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, USP, Ribeirão Preto, SP, Brazil.* * *These authors contributed equally to this work.*

**Objective:** Current treatments for schizophrenia (SZ) are often not effective for all symptoms, with sex-dependent effects poorly understood. Cannabidiol (CBD) and sodium nitroprusside (SNP) have emerged as potential prophylactic options. We evaluated their efficacy in preventing positive, negative, and cognitive deficits in a ketamine (KET) rodent model of SZ in both sexes.
**Methods:** Wistar rats were pretreated with CBD and SNP (alone or combined) during brain development (postnatal days 12-32). After 10 days, SZ-like deficits were induced via KET. Behaviors were assessed using the open field test (OFT), sucrose preference test (SPT), and novel object recognition (NOR) test.
**Results:** KET induced sex-dependent effects: females showed greater hyperlocomotion and long-term NOR memory deficits, while males exhibited reduced sucrose preference and short-term NOR impairments. CBD or SNP alone had limited efficacy, but their combination reduced hyperlocomotion and prevented NOR deficits in both sexes. Multivariate analysis revealed superior prophylactic effects in females, with unsupervised clustering showing distinct behavioral phenotypes between sexes.
**Conclusion:** This study provides the first preclinical evidence of sex-dependent prophylactic efficacy of CBD-SNP in a SZ model, suggesting a promising therapeutic strategy.

**Keywords:** Schizophrenia; sex; ketamine; cannabidiol; sodium nitroprusside

## Introduction

Schizophrenia (SZ) is a debilitating neuropsychiatric disorder characterized by positive and negative symptoms, as well as cognitive deficits.[1] While antipsychotic medications alleviate positive symptoms, they are less effective for cognitive impairments and are often associated with side effects.[2] Moreover, the symptoms of SZ and the efficacy of antipsychotics vary by sex: men tend to exhibit more negative symptoms and have higher rates of treatment than non-responders, while women are more prone to positive symptoms and antipsychotic side effects.[3] Interestingly, women are more affected by ketamine (KET)-induced psychotic symptoms than men.[4,5] These findings notwithstanding, few studies have examined sex-based differences in the efficacy of antipsychotics.[6]

Recent research suggests pharmacological interventions during brain development may offer a promising strategy to prevent SZ symptoms, recognizing SZ as a neurodevelopmental disorder with potentially preventable later-stage symptoms.[7,8] Early treatment with atypical

Correspondence: Isabella Caroline da Silva Dias, Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes, 3900, CEP 14049-900, Ribeirão Preto, SP, Brazil
E-mail: isadias@usp.br
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antipsychotics in high-risk individuals has been shown to reduce transition rates to psychosis and improve positive symptoms.[9] Even earlier brain development stages might present a critical window for prevention, though early antipsychotic treatment is discouraged due to safety concerns.[10,11] Additionally, there is a lack of evidence to support the preventive effect of pharmacological interventions during brain development in SZ.

The rodent KET model is typically used as a translational pharmacological model of SZ. It is commonly used to study SZ and its treatment, as KET injections induce positive-like symptoms and cognitive deficits, including hyperlocomotion and impairments in the novel object recognition (NOR) task.[12-15] This model is sensitive to typical and atypical antipsychotics,[16] making it valuable for investigating new treatments. Despite evidence that female rats are more sensitive than males to KET (e.g., hyperlocomotion in acute/chronic dosing), preclinical studies often exclude females, as do clinical trials.[17]

Cannabidiol (CBD) and sodium nitroprusside (SNP) have emerged as potential treatments for SZ.[18] CBD, a non-psychotomimetic compound from *Cannabis sativa*, has shown safe antipsychotic effects in humans and rodents and improves blood oxygen level-dependent (BOLD) signals in mesolimbic structures in high-risk psychosis patients.[19,20] Furthermore, chronic CBD treatment during adolescence decreases hyperlocomotion and memory impairments in SZ animal models[21,22] SNP, a nitric oxide (NO) donor, reverses positive symptoms in humans and hyperlocomotion in rodents, and it prevents SZ-like behaviors during adolescence in animal models.[23-26] Clinical studies suggest higher efficacy of CBD and SNP as antipsychotics in younger subjects,[27,28] and their combination presents an intriguing avenue for research.[18] However, the sex-specific prophylactic effects of CBD and SNP, alone or combined, during SZ development in animal models remain unexplored.

## Methods

### *Animals*

Wistar rats (males, n=77; females, n=71) started treatment on postnatal day 12 (P12). The pups were breastfed by their mother during the 21-day pretreatment period and were then grouped in cages of four animals until the experiments began. Upon weaning, pups were sex-segregated and housed in separate cages. Littermates were not assigned to the same experimental group. All procedures followed the guidelines of the Conselho Nacional de Controle de Experimentação Animal and were approved by the local ethics committee (Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; protocol: 62/2016).

### *Drugs*

CBD (BSPG-Pharm, Sandwich, United Kingdom; 1 mg/kg i.p.) was diluted in Tween 80 and in saline (SAL) (2% of Tween 80 and 98% of NaCl 0.9% solution). SNP (Cristália, Itapira, Brazil; 2.5 mg/kg i.p.) was freshly dissolved in 5% glucose. All pretreatment solutions were injected in a volume of 1 mL/kg/day. Vehicle (VEH) pretreatment consisted of SAL (0.9% w/v, Isofarma, Eusébio, Brazil) administered for 21 days, except every 5 days, when we administered a glucose injection (5% w/v, Isofarma, Eusébio, Brazil) instead of SAL. During the treatment, subjects received SAL or KET (Cristália, Itapira, Brazil; 30 mg/kg i.p.) diluted in 0.9% NaCl to a volume of 10 ml/kg/day. The treatment regimen and dosages were determined based on established studies.[21,25,28,29] The number of rats per group is shown in Table 1.

### *Experimental design*

The experimental design was the same for both sexes and is summarized in Figure 1A. First, P12 rats were subjected to pretreatment (VEH, CBD, SNP, or both [CBD-SNP] once daily for 21 days). After a 10-day interval, the animals received SAL 0.9% or KET treatment once daily for 5 days, followed by the behavioral tests.

### *Behavioral tests*

#### Open field test

Locomotor activity was evaluated in the OFT on the last day of treatment. Thirty minutes after the last SAL or KET injection, rats were placed in the center of the OFT apparatus for 20 min (Figure 1B). The OFT was performed and analyzed as described previously by our group.[23]

#### Sucrose preference test

The SPT was conducted over 3 days (P48-P50) (Figure 1C) as described previously by our group.[23] The subjects were placed alone in cages with free access to one bottle of water and one bottle of 1% w/v sucrose solution. SPT was measured as the ratio of sucrose consumed to total fluid consumed and values converted to a percentage.

#### Novel object recognition test

The NOR test was also based on a protocol performed previously by our group[30] and was applied on the same days as the SPT (Figure 1D). Briefly, the NOR protocol consisted of three phases: habituation on day 1 (P48), training and test 1 on day 2 (P49), and test 2 on day 3 (P50).

**Table 1** Distribution of male and female rats per experimental group

| Group | Males (n) | Females (n) |
|---|---|---|
| Control | 10 | 10 |
| KET | 8 | 10 |
| CBD | 10 | 12 |
| CBD-KET | 12 | 9 |
| SNP | 10 | 8 |
| SNP-KET | 9 | 8 |
| CBD-SNP | 9 | 8 |
| CBD-SNP-KET | 9 | 6 |

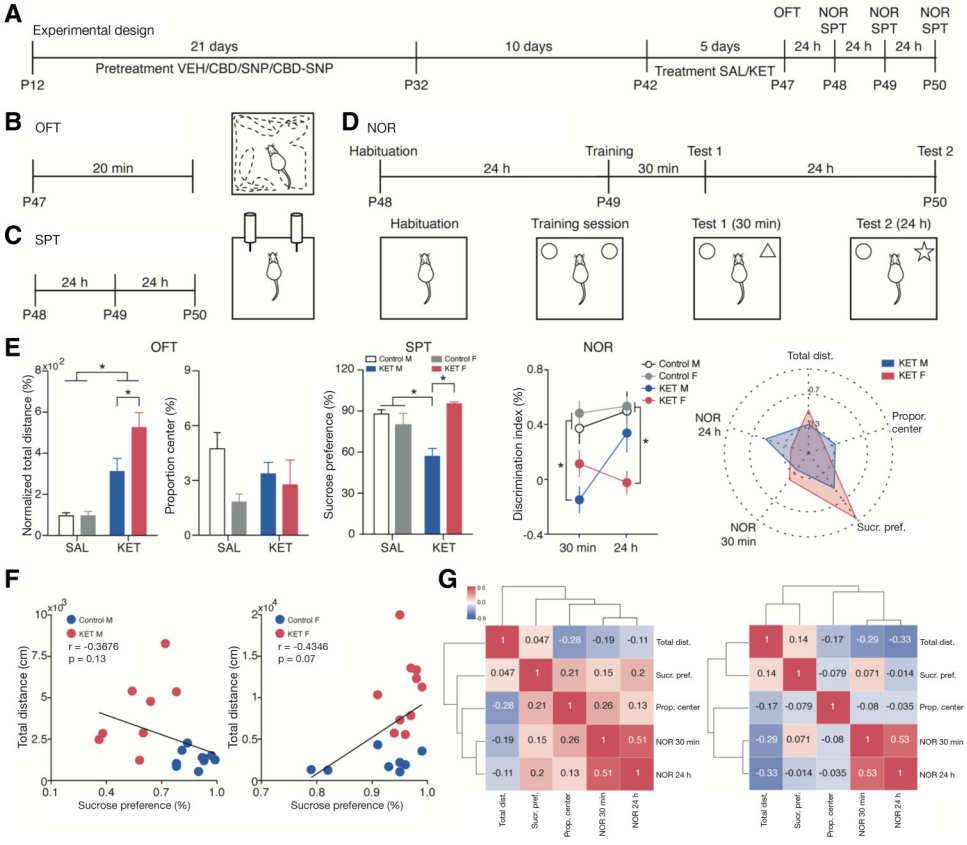



**Figure 1** Experimental design and sex-dependent effects of KET. A) Experimental design. B) OFT: After the last SAL or KET injection, locomotor activity was evaluated in the OFT by total distance traveled and proportion of time in the center of the arena. C) SPT: Rats were individualized in cages containing two bottles, one with water and one with sucrose solution, for 3 days. D) NOR: The NOR test consisted of three phases: habituation, training following test 1, and test 2. E) Sex-dependent effects of KET treatment. F) Behavioral feature correlations in males and females after KET treatment. Pearson's correlation between total distance and sucrose consumption in male rats (left) and female rats (right). G) Correlation between behavioral features, including all experimental groups. Right: correlogram of behavioral features in all-male groups. Left: correlogram of behavioral features in all-female groups. CBD = cannabidiol; KET = ketamine; NOR = novel object recognition; OFT = open field test; SAL = saline; SNP = sodium nitroprusside; SPT = sucrose preference test; VEH = vehicle. * $p < 0.05$.

In the training session, rats were allowed to explore two equal objects. Thirty minutes (test 1) and 24-h (test 2) after the training section, a new object replaced one of the previous objects, and the animals were allowed to explore them. In the NOR task, object exploration was defined by the time spent sniffing or touching the object (t), and NOR performance was evaluated by the discrimination index (DI).[31] Based on previous work which considered individual differences in the NOR protocol,[32] DI was calculated as: DI = ($t_{test}$ – $t_{habit}$), where $t_{test}$ = ($t_{novel}$ – $t_{familiar}/t_{total}$) and $t_{habit}$ = ($t_{object}$ A – $t_{object}$ A'/$t_{total}$).

*Data analysis*

Radar chart

All behavioral measures were used to compose radar charts, which were constructed by performing a min-max normalization between each behavioral variable for all the experimental groups: Z = [x – min(x)/max(x) – min(x)]. Radar charts are useful for presenting multivariate data and assessing the profile of treatments, both in clinical and in basic research.[33]

Multivariate analysis

Multivariate analysis was performed using the MATLAB, Scikit-learn,[34] and Yellow Brick[35] packages in Python. Pearson's correlation was used to infer a bivariate linear relationship between behavioral attributes. For correlograms, the behavioral features were sorted by hierarchical agglomerative clustering using the average linkage method and correlations as metrics. Specifically, we eliminated multivariate outliers for correlation analysis that could indicate spurious correlations by applying the local outlier factor (LOF).[36] The LOF indicated two outliers for the female group, while in the males, no outlier was detected. For the rest of the multivariate analysis, no outliers were excluded.

### Linear discriminant analysis (LDA)

We used LDA for dimensionality reduction while maintaining class-discriminatory information. The objective of LDA is to find a projection – linear combinations of original space features – that maximizes differences between different class means, while minimizing the within-class variation.[37]

The behavioral features were z-scored, separating males from females, using the Control, KET, CBD-KET, SNP-KET, and CBD-SNP-KET groups and eliminating redundant features (such as distance and velocity). We performed a multivariate normality test as described by Trujilo-Ortiz et al.[38] Female and male groups did not reject the null hypothesis that the sample came from a multivariate normal distribution ($p > 0.05$). We used the Scikit-Learn algorithm[34] with a singular value decomposition solver and three components for LDA dimensionality reduction. Original data were projected in the first two LDA dimensions (LD1 and LD2). For each feature, we calculated the LDA loadings as the scaled eigenvectors and explained variance as the scaled eigenvalues. Distances between groups in the two-dimensional LDA were measured by the Euclidean distance between every observation of a treatment group and all the observations of the KET group. This calculation gave us a distribution of distances that were compared using the Kolmogorov-Smirnov test.

### Classification

Logistic regression was used to create a classification model in which subjects were classified as either similar to the control group or to the KET group, based on the discriminant components from LDA. Logistic regression was chosen as it makes fewer assumptions about the data, and LASSO regularization was used to avoid overfitting. Other algorithms, such as support vector machines and k-nearest neighbors, produced similar results (Supplementary Figure S1). To compare the classification probabilities of the animals, the Jensen-Shannon divergence between the probability distributions of the control group and the others was calculated, and the results compared using one-way analysis of variance (ANOVA).

### Clusterization

We performed unsupervised clusterization analysis using an agglomerative hierarchical algorithm to establish the behavioral relationship between subjects. We used the ward method to define clusters, and the metric used was Euclidean distance. We used this approach for LDA scores and original variables. An optimal number of clusters was estimated using the Elbow method.[39] However, the final definition was based on parsimonious interpretability of the results (Supplementary Figure S2).

### *Statistical analysis*

Levene's and Lilliefors tests were used to evaluate whether the data were parametric. Data from OFT and SPT were analyzed by two-way ANOVA (treatment vs. sex or pretreatment vs. treatment). NOR data were analyzed by three-way mixed-model ANOVA with Trial as the within-subjects factor (pretreatment vs. treatment vs. time). Multiple comparisons were performed using the Newman-Keuls (NK) post hoc test. The Kruskal-Wallis test, following Dunn's test, analyzed the divergence of the probability distribution of each sex. All results are expressed as mean $\pm$ standard error of the mean (SEM), and statistical significance was set at $p < 0.05$.

## Results

### *Distinctive sex-dependent effects of KET*

To assess sex-dependent effects of KET on behavior, we compared control and experimental groups of males (M) and females (F) (Control-M, Control-F, KET-M, KET-F, n=8-10 per group). KET induced hyperlocomotion in both sexes, with females exhibiting higher levels (treatment-sex effect: $F[1.34] = 5.553$, $p < 0.05$). No sex differences were found in the time spent in the center (Sex effect: $F[1.34] = 4.145$, $p > 0.05$). In males, KET reduced sucrose consumption (treatment-sex effect: $F[1.34] = 22.26$, $p < 0.01$). Additionally, KET decreased DI in males in the NOR 30-min test and in females in the NOR 24-h test (treatment-sex-time effect: $F[1.34] = 6.006$, $p < 0.05$; Figure 1E).

Interestingly, females showed a positive correlation between total distance traveled and sucrose consumption (positive: $r = 0.4346$, $p = 0.07$), while males did not ($r = -0.3676$, $p = 0.13$) (Figure 1F). Bivariate correlations indicated a sex-differential relationship between behavioral features, though not statistically significant (Figure 1G).

### *Prophylactic effects of CBD combined with SNP decreased positive-like and cognitive impairments in males*

We assessed the prophylactic efficacy of CBD and/or SNP on KET-induced impairments in male rats (n=8-12 per group) (Figure 2). CBD pretreatment did not prevent hyperlocomotion (treatment effect: $F[1.36] = 17.50$, $p < 0.01$; NK significance: Control vs. KET, Control vs. CBD-KET, CBD vs. KET). However, it increased the time spent in the center (pretreatment effect: $F[1.36] = 5.343$, $p < 0.05$; treatment effect: $F[1.36] = 6.974$, $p < 0.05$; NK significance: Control vs. CBD, CBD vs. KET, CBD vs. CBD-KET) and did not affect sucrose consumption. Additionally, CBD prevented KET-induced deficits in the 30-min NOR test (time-treatment effect: $F[1.38] = 4.124$, $p < 0.05$; time-pretreatment effect: $F[1.38] = 8.082$, $p < 0.01$; NK significance: Control NOR 30 vs. KET NOR 30, CBD NOR 30 vs. KET NOR 30, CBD-KET NOR 30 vs. KET NOR 30) (Figure 2A).

Similar to CBD, SNP pretreatment did not prevent KET-induced hyperlocomotion (pretreatment-treatment effect: $F[1.31] = 4.164$, $p < 0.05$; NK significance: Control vs. KET, SNP vs. KET) or affect the time spent in the center. However, SNP decreased sucrose consumption (pretreatment effect: $F[1.31] = 6.238$, $p < 0.05$; treatment

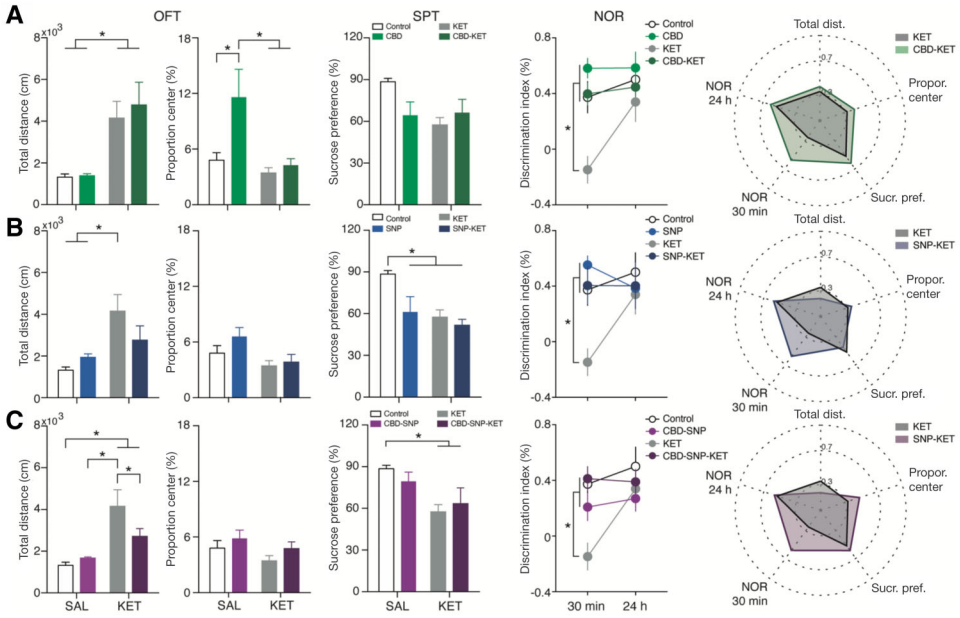



**Figure 2** Prophylactic effects of CBD and SNP pretreatment on SZ-like impairments in males. A) CBD pretreatment prevented KET-induced deficits in the 30-min NOR test. B) SNP pretreatment prevented deficits in the 30-min NOR test, although it decreased sucrose consumption when administered alone. C) Pretreatment with CBD and SNP decreased KET-induced positive-like and cognitive impairments (Control, n=10; KET, n=8; CBD, n=10; CBD-KET, n=12; SNP, n=10; SNP-KET, n=9; CBD-SNP, n=9; CBD-SNP-KET, n=9). CBD = cannabidiol; KET = ketamine; NOR = novel object recognition; OFT = open field test; SAL = saline; SNP = sodium nitroprusside; SPT = sucrose preference test; SZ = schizophrenia. * $p < 0.05$.

effect: $F[1.31] = 9.314$, $p < 0.01$; NK significance: Control vs. SNP, Control vs. KET, Control vs. SNP-KET). SNP also showed prophylactic efficacy in the 30-min NOR test (time-pretreatment effect: $F[1.30] = 11.53$, $p < 0.05$; time-treatment effect: $F[1.30] = 5.174$, $p < 0.05$; NK significance: Control NOR 30 vs. KET NOR 30; SNP NOR 30 vs. KET NOR 30, SNP-KET NOR 30 vs. KET NOR 30) (Figure 2B).

CBD-SNP pretreatment reduced KET-induced hyperlocomotion (pretreatment-treatment effect: $F[1.32] = 4.817$, $p < 0.05$; NK significance: Control vs. KET, KET vs. CBD-SNP-KET, Control vs. CBD-SNP-KET, CBD-SNP vs. KET) without affecting the time spent in the center. In the SPT, CBD-SNP pretreatment did not reduce sucrose consumption like SNP pretreatment, nor did it prevent KET's effects (treatment effect: $F[1.32] = 10.93$, $p < 0.01$; NK significance: Control vs. KET, Control vs. CBD-SNP-KET). However, CBD-SNP pretreatment prevented KET-induced deficits in the 30-min NOR test (pretreatment-treatment-time effect: $F[1.32] = 5.422$, $p < 0.05$; NK significance: Control NOR 30 vs. KET NOR 30, CBD-SNP NOR 30 vs. KET NOR 30, CBD-SNP-KET NOR 30 vs. KET NOR 30) (Figure 2C).

### *Prophylactic effects of CBD combined with SNP decreased positive-like and cognitive impairments in females*

In females, KET-induced behavioral impairments were more pronounced than in males, with CBD and SNP pretreatment, particularly in combination, proving more effective (Figure 3). CBD pretreatment reduced hyperlocomotion (pretreatment-treatment effect: $F[1.37] = 11.28$, $p < 0.01$; NK significance: Control vs. KET, Control vs. CBD-KET, CBD vs. KET, CBD vs. CBD-KET, KET vs. CBD-KET) but did not increase center time. It also decreased sucrose preference after KET treatment (pretreatment-treatment effect: $F[1.37] = 5.565$, $p < 0.05$; NK significance: Control vs. CBD-KET, CBD vs. KET, KET vs. CBD-KET) and failed to prevent deficits in the 24-H NOR test (treatment effect: $F[1.36] = 15.22$, $p < 0.01$; pretreatment-treatment effect: $F[1.36] = 8.052$, $p < 0.01$; NK significance: Control NOR 30 vs. KET NOR 30, Control NOR 24 vs. KET NOR 24, Control NOR 24 vs. CBD NOR 24, Control NOR 24 vs. CBD-KET 24) (Figure 3A).

SNP pretreatment in females decreased hyperlocomotion (pretreatment-treatment effect: $F[1.32] = 8.474$, $p < 0.01$; NK significance: Control vs. KET, SNP vs. KET, KET vs. SNP KET) without effects in the proportion of time spent in the center. As in males, SNP pretreatment decreased sucrose consumption (pretreatment effect: $F[1.32] = 22.98$, $p < 0.01$; NK significance: Control vs. SNP, Control vs. SNP-KET, SNP vs. KET, KET vs. SNP-KET) and did not prevent KET deficits in the NOR test (pretreatment-treatment effect: $F[1.32] = 6.634$, $p < 0.05$; NK significance: Control NOR 30 vs. KET NOR 30, SNP NOR 30 vs. KET NOR 30, Control NOR 24 vs. KET NOR 24) (Figure 3B).

In females, combined CBD and SNP pretreatment reduced hyperlocomotion (pretreatment-treatment effect:

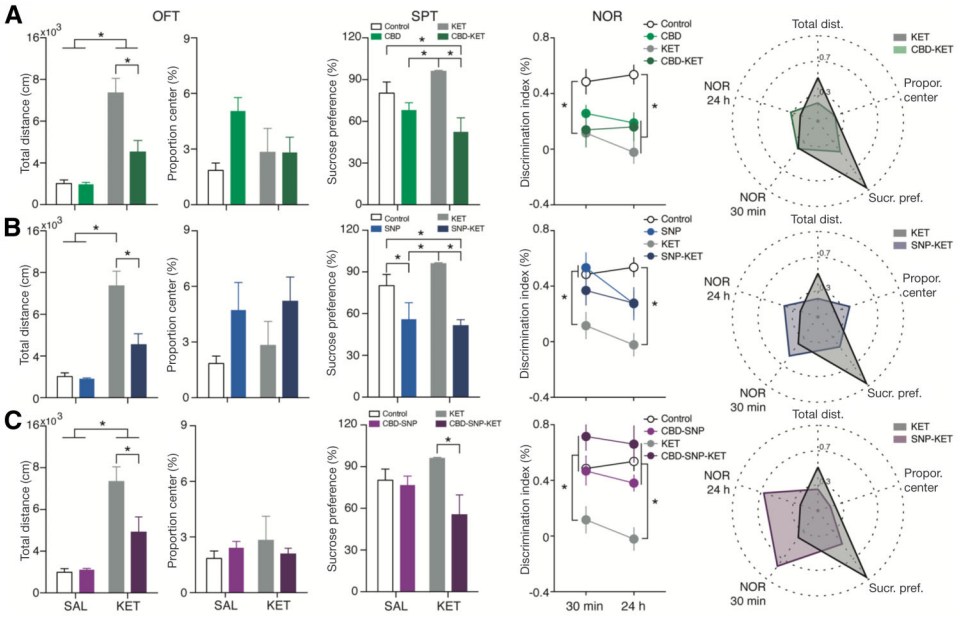



**Figure 3** Prophylactic effects of CBD and SNP pretreatment on SZ-like impairments in females. A) CBD pretreatment prevented KET-induced deficits in the OFT and the 30-min NOR test. B) SNP prevented KET-induced deficits in the OFT, although it decreased sucrose consumption when administered alone. C) Pretreatment with CBD and SNP prevented KET-induced positive-like symptoms, sucrose preference, and cognitive impairments. (Control, n=10; KET, n=10; CBD, n=12; CBD-KET, n=9; SNP, n=8; SNP-KET, n= 8; CBD-SNP, n=8; CBD-SNP-KET, n=6). CBD = cannabidiol; KET = ketamine; NOR = novel object recognition; OFT = open field test; SAL = saline; SNP = sodium nitroprusside; SPT = sucrose preference test; SZ = schizophrenia. * $p < 0.05$.

$F[1.30] = 6.524$, $p < 0.05$; NK significance: Control vs. KET, Control vs. CBD-SNP-KET, CBD-SNP vs. KET, CBD-SNP vs. CBD-SNP-KET, KET vs. CBD-SNP-KET) without affecting the time spent in the center. It also improved cognitive performance in the NOR test (pretreatment-treatment effect: $F[1.30] = 30.09$, $p < 0.01$; NK significance: Control NOR 30 vs. KET NOR 30, CBD-SNP NOR 30 vs. KET NOR 30, CBD-SNP-KET NOR 30 vs. KET NOR 30, Control NOR 24 vs. KET NOR 24, CBD-SNP NOR 24 vs. KET NOR 24, CBD-SNP-KET NOR 24 vs. KET NOR 24) and reduced sucrose preference after KET treatment (pretreatment-treatment effect: $F[1.30] = 5.844$, $p < 0.05$; NK significance: KET vs. CBD-SNP-KET) (Figure 3C).

*Sex-dependent efficacy of CBD-SNP prophylactic effects in KET model*

We applied LDA for dimensionality reduction to evaluate and compare treatment efficacy, identifying behavioral features that distinguish groups into males and females (Figure 4). In males, LD1 discriminated control and KET groups, correlating with total distance (Pearson's correlation with original variables, $R^2 = 0.63$, $p < 0.01$), reduced sucrose consumption ($R^2 = -0.55$, $p < 0.01$), and cognitive deficits in the 30-min NOR test ($R^2 = -0.63$, $p < 0.01$). LD2 was mainly associated with decreased performance in the 30-min NOR test ($R^2 = -0.66$, $p < 0.01$) and discriminated against part of the treated animals (Figure 4A). The classifier based on LD1 and LD2 explained 90.38% of the variance in males (Supplementary Figure S2A). Similar efficacy was observed across treatment groups for classification as control-like animals (41.66% CBD-KET, 75% SNP-KET, 55.55% CBD-SNP-KET) (Figure 4B), with similar LD1 and LD2 scores across groups (Supplementary Figure S2B). No significant difference was found in probability distribution divergence between the KET and treatment groups ($H[4.37] = 7.904$, $p > 0.05$) (Figure 4C), nor in the cumulative distribution function of Euclidean distances (Kolmogorov-Smirnov test, $p > 0.05$) (Supplementary Figure S2B).

In females, LDA distinguished the KET group from controls by LD1, that is associated with low locomotion ($R^2 = -0.72$, $p < 0.01$) and sucrose consumption ($R^2 = -0.45$, $p < 0.01$), and higher performance in the NOR 30-min ($R^2 = -0.58$, $p < 0.01$) and NOR 24-h tests ($R^2 = -0.76$, $p < 0.01$). LD2 was correlated with low sucrose consumption ($R^2 = -0.77$, $p < 0.01$) and increased center time ($R^2 = 0.49$, $p < 0.01$), primarily discriminating treated animals (Figure 4D). LD1 and LD2 explained 88.59% of the variance in females (Supplementary Figure S2A). The logistic regression model indicated that more animals in the CBD-SNP-KET group were classified as control (44.44% CBD-KET, 50% SNP-KET, 100% CBD-SNP-KET) (Figure 4E). The CBD-SNP-KET group showed a higher LD1 score, reflecting distinct behavior (Supplementary Figure S2B). The probability distribution

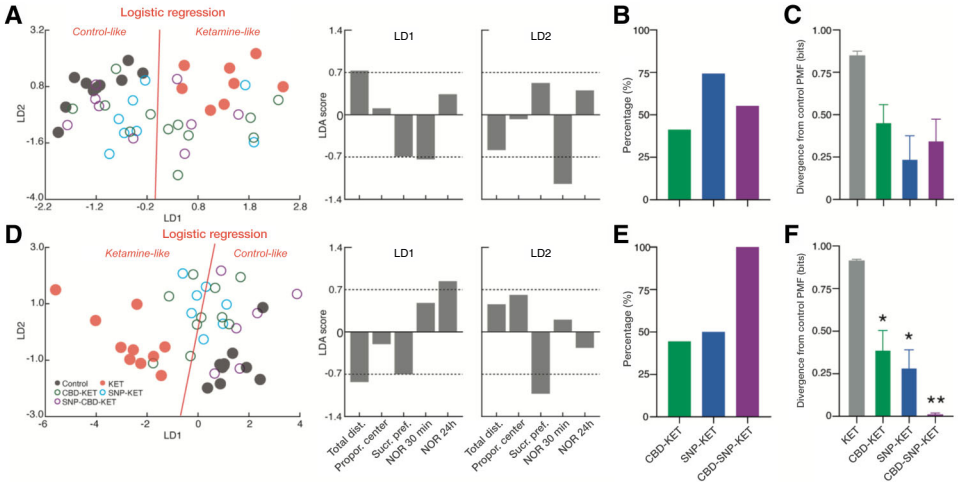



**Figure 4** Multivariate effects of treatment in males and females. A) LDA in males. B) Percentage of male animals classified as control. C) The comparative divergence between control probability distribution suggests proximity of behavioral phenotypes of the KET and pretreatment groups. D) LDA in females. E) Percentage of female animals classified as control. All females in the CBD-SNP-KET group are classified as control. F) Pretreatment female groups present a distinct comparative divergence from the control group, especially the CBD-SNP-KET group. CBD = cannabidiol; KET = ketamine; LDA = linear discriminant analysis; LD1 = dimension 1 of LDA; LD2 = dimension 2 of LDA; NOR = novel object recognition; PMG = probability mass function; SAL = saline; SNP = sodium nitroprusside; SZ = schizophrenia. * $p < 0.05$; ** $p < 0.01$.

of all treatment groups diverged from the KET group ($H[4.33] = 21.96$, $p < 0.05$), with the CBD-SNP-KET group showing significant divergence from KET ($H[4.33] = 21.96$, $p = 0.0001$), exhibiting a greater distance from KET subjects compared to SNP-KET and CBD-KET groups, although SNP showed a greater distance than CBD (Kolmogorov-Smirnov test, $p < 0.01$) (Supplementary Figure S2C).

### *Sex dependence of distinct behavioral phenotypes*

We applied unsupervised hierarchical clustering to identify subpopulations of treated animals based on behavioral phenotype, independent of group labels, aiming for a more descriptive approach.

In males, four clusters were identified based on LDA scores (Figure 5A and Supplementary Figure S3A). Cluster 1 showed low locomotion and cognitive scores, comprising a mix of groups. Cluster 2 displayed a control-like phenotype and included control and treated animals. Cluster 3, predominantly composed of CBD-treated animals, was characterized by improved cognitive performance. Cluster 4 exhibited a psychotic-like phenotype, with increased locomotion, reduced sucrose consumption, and low NOR 1 scores, and was mainly composed of KET animals. Confidence intervals for male clusters are summarized in Supplementary Table S1.

In females, clustering revealed three distinct phenotypes (Figure 5E and Supplementary Figure S3B). Cluster 1 represented KET animals, with increased locomotion, higher sucrose consumption, and cognitive deficits. Cluster 2, with control-like traits, consisted of control animals and part of the CBD-SNP-KET group. Cluster 3, an intermediary phenotype, included mainly CBD- and SNP-treated animals, showing improved cognitive performance and reduced hyperlocomotion but lower sucrose consumption. Confidence intervals for female clusters are summarized in Supplementary Table S2.

An unsupervised clustering of all groups from both sexes revealed three clusters (Supplementary Figure S4). Cluster 1, typical of control animals, included the majority of control subjects (80% in both sexes) and 50% of CBD-SNP-KET females. Cluster 2 represented an intermediate phenotype with good cognitive performance, reduced locomotion, and decreased sucrose consumption. It contained most of the KET-male group and some treated animals. Cluster 3, reflecting KET-like impairments, included the majority of KET-F (90%) and CBD-KET-F (66.66%) animals, as well as part of KET-M and SNP-KET-F groups (37.5% for both).

## Discussion

Considering preliminary data in the literature, we hypothesized that the combination of CBD and SNP would be an interesting prophylactic treatment to be investigated in a KET model of SZ in both sexes. In general, KET elicited sex-dependent impairments, but both male and female rats exhibited hyperlocomotion and memory impairments. Females had a better pharmacological response profile than males to CBD-SNP pretreatment. To our knowledge, this is the first evidence of a sex-dependent KET response and prophylactic efficacy of CBD and SNP in an animal model of SZ.

Basic research studies have demonstrated sex differences in animal models.[4,40] Similar to our results, other studies show that female rats presented higher locomotor activity,[41] and male rats presented decreased sucrose

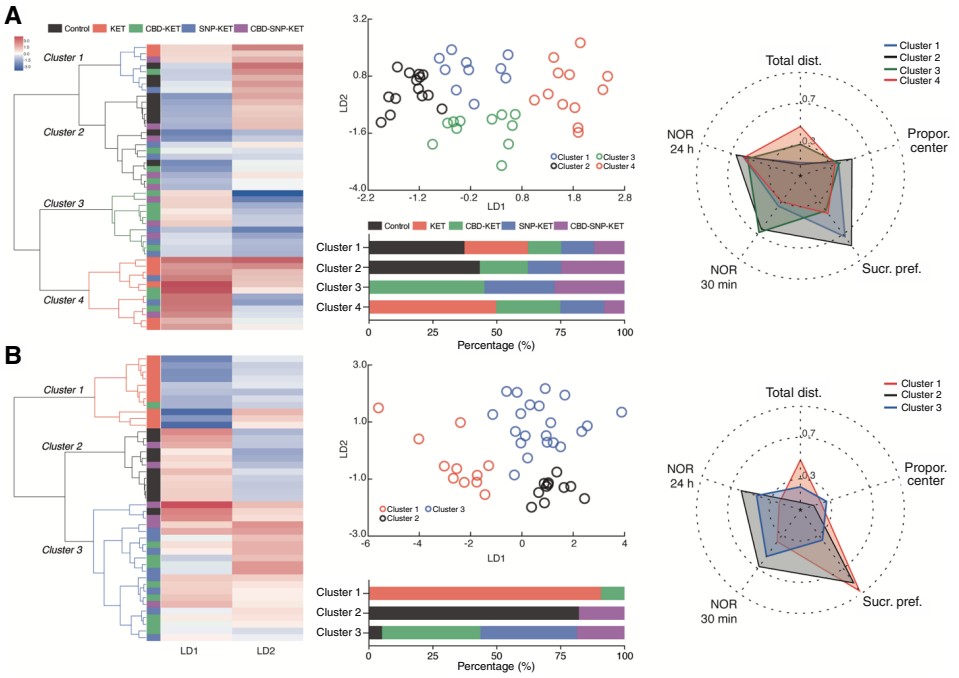



**Figure 5** Identification of clusters (Clus) using behavioral features. A) Dendrogram of the four-cluster formation in males and their LDA analysis components followed by their stacked bars and radar plot. B) Dendrogram of the three-cluster formation in females and their LDA analysis components followed by their stacked bars and radar plot. Stacked bar plot representing the percentage of animals from each group in the identified clusters. Radar plot representing the mean values of the normalized behavioral features by cluster in males. CBD = cannabidiol; KET = ketamine; LDA = linear discriminant analysis; LD1 = dimension 1 of LDA; LD2 = dimension 2 of LDA; NOR = novel object recognition; SNP = sodium nitroprusside.

consumption,[42] but it was not investigated in a KET model of SZ. In females, total distance traveled positively correlated with sucrose preference, whereas in males, the opposite occurred (Figure 1). This suggests that females exhibit more addictive-like behavior, with increased hyperlocomotion and sucrose consumption, while males display typical KET symptoms, including psychosis and anhedonia-like behavior. In general, females responded better to the pretreatments tested, which is interesting from a translational perspective, considering that women benefit more from traditional antipsychotics than men.[5,43]

There is long-standing evidence of antipsychotic effects of CBD.[44] When CBD is administered chronically to younger subjects, both positive-like symptoms and cognitive impairments improve substantially. Peres et al.[45] described that CBD treatment for 30 days during peri-adolescence decreased hyperlocomotion induced by maternal immune activation with poly I:C. Similarly, CBD treatment prevented hyperlocomotion, prepulse inhibition, and contextual fear conditioning deficits in the SHR model of SZ.[21] Osborne et al.[22] found that twice-daily CBD administration for 3 weeks reversed cognitive and working memory deficits, as shown in the NOR and rewarded T-maze tests. Recently, Brakatselos et al.[46] also investigated the antipsychotic effects of CBD in a repeated KET administration model. The study revealed that CBD exerted region-specific effects, normalizing cortico-hippocampal and corticostriatal network activity, likely through endocannabinoid system modulation and E/I imbalance correction. However, the findings of this study reveal that CBD pretreatment reduced hyperlocomotion only in females, while cognitive impairments were prevented solely in male rats. Interestingly, the first clinical evidence of the antipsychotic effects of CBD was observed in a young woman.[47]

Several studies have described antipsychotic-like effects of SNP as well.[23,26] Our group conducted the first clinical work reporting the antipsychotic effects of SNP, demonstrating that a single infusion was sufficient to improve positive, negative, and cognitive symptoms of SZ.[25] In animal models of SZ, SNP pretreatment reversed KET-induced hyperlocomotion for up to a week after administration.[24] Additionally, SNP treatment during peri-adolescence prevented behavioral abnormalities in a SHR model.[26] While SNP was effective in reducing hyperlocomotion, it did not reverse cognitive deficits in some studies.[23] However, in the LPS-induced neuroinflammation model, SNP reversed memory and learning deficits in the Morris water maze test.[48] Conversely, SNP pretreatment was insufficient to reduce psychotic-like behavior in a model using MK-801, a non-KET NMDA antagonist.[29] Our data indicated that SNP pretreatment prevented hyperlocomotion only in females, while cognitive impairments were reduced in both sexes.

The mechanisms of action of CBD and SNP are not fully understood, but evidence suggests they have antipsychotic mechanisms. CBD may reverse or prevent KET-induced synaptic plasticity impairments by affecting neuronal activation and synaptic plasticity in cortico-mesolimbic circuits.[49-51] It also promotes hippocampal neurogenesis, activates 5-$HT_{1A}$ receptors, and inhibits anandamide reuptake.[52] The antipsychotic effect of SNP is mainly associated with its ability to donate NO,[18,26] which may modulate molecular events affecting *N*-methyl-D-aspartate (NMDA) receptor function.[53] Recent evidence suggests that SNP decreases Ndel1, a potential biomarker for both pathogenesis and treatment prognosis in patients with SZ.[54] Further research is needed to explore the physiological and molecular changes associated with the prophylactic effects of CBD and SNP.

Our multivariate analysis is exploratory, as more data would be needed for stronger conclusions. However, it provides valuable insights into how variables interact beyond average values, revealing previously unrecognized groupings and behavioral clusters. It also highlights treatment and sex differences, showing that in females, the control behavior phenotype is closer to that of CBD-SNP treatment, while in males, the effect is milder (Figure 4). Additionally, there is significant variability in behavior even within the same treatment group (Figures 4 and 5), with KET injections producing distinct phenotypes in males and females (Figure 5). These findings suggest that females are more affected by KET, and that the therapeutic response to pretreatments is weaker in males. This supports the importance of multivariate analyses in basic research to capture individual variability not evident in univariate analyses.[55]

In conclusion, we propose a novel therapeutic approach for SZ-like symptoms in both sexes, emphasizing the translational relevance of sex differences in SZ. We obtained optimistic results with a combination of CBD and SNP – two drugs different from current antipsychotics and with a safer side-effect profile – when given as pretreatment. We have also shown that pretreatment after pregnancy and before preadolescence could be an exciting approach for investigating new proposals for SZ treatment. However, it is possible that the observed sex-specific effects stem from pharmacokinetic differences, such as variations in metabolism, plasma levels, an interaction between CBD and SNP, or blood-brain barrier permeability to CBD and SNP, which should be addressed in future studies.

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## Disclosure

AWZ, JAC, and JECH are co-inventors of the patent "Cannabinoid-containing oral pharmaceutical composition, method for preparing and using the same," Instituto Nacional de Propriedade Industrial (INPI) on September 16, 2016 (BR 112018005423-2). AWZ, JAC, and JECH are co-inventors of the patent "Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023," Def. US number Reg. 62193296; July 29, 2015; INPI on August 19, 2015 (BR1120150164927; Mechoulam R, Zuardi AW, Kapczinski F, Hallak JEC, Guimarães FS, Crippa JAS, Breuer A). Universidade de São Paulo (USP) has licensed this patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1) and has an agreement with Prati-Donaduzzi to "develop a pharmaceutical product containing synthetic CBD and prove its safety and therapeutic efficacy in the treatment of epilepsy, SZ, Parkinson's disease, and anxiety disorders." JAC and JECH have received travel support to attend scientific meetings and personal consultation fees from BSPG-Pharm. The other authors report no conflicts of interest.

## Data availability statement

The data that support this study are available in the body of the paper and/or supplementary materials.

## Author contributions

DBAP: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing.
MTR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.
RNR: Formal analysis, Methodology, Writing – original draft, Writing – review & editing.
JEPS: Conceptualization, Methodology, Project administration.
JPL: Conceptualization, Project administration.
SMD: Conceptualization, Writing – review & editing.
LHD: Investigation, Methodology, Writing – review & editing. AWZ: Conceptualization, Visualization. RGS: Conceptualization, Supervision.
VCA: Validation, Visualization. JA: Methodology, Validation.
JAC: Conceptualization, Investigation, Validation. GGA: Data curation, Writing – review & editing.
JECH: Conceptualization, Data curation, Formal analysis,

Funding acquisition, Project administration, Resources, Validation.
ICSD: Data curation, Formal analysis, Investigation, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.
All authors have read and approved of the final version to be published.

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