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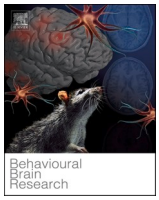

Short communication

# Decreased activation of parvalbumin interneurons in the medial prefrontal cortex in intact inbred Roman rats with schizophrenia-like reduced sensorimotor gating

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ABSTRACT

Prepulse inhibition (PPI) allows assessing schizophrenia-like sensorimotor gating deficits in rodents. Previous studies indicate that PPI is modulated by the medial prefrontal cortex (mPFC), which is in agreement with our findings showing that PPI differences in the Roman rats are associated with divergences in mPFC activity. Here, we explore whether differences in PPI and mPFC activity in male Roman rats can be explained by (i) differences in the activation (c-Fos) of inhibitory neurons (parvalbumin (PV) interneurons); and/or (ii) reduced excitatory drive (PSD-95) to PV interneurons. Our data show that low PPI in the Roman high-avoidance (RHA) rats is associated with reduced activation of PV interneurons. Moreover, the RHA rats exhibit decreased density of both PV interneurons and PSD-95 puncta on active PV interneurons. These findings point to reduced cortical inhibition as a candidate to explain the schizophrenia-like features observed in RHA rats and support the role of impaired cortical inhibition in schizophrenia.

## 1. Introduction

Sensorimotor gating, which is a process to filter out relevant from irrelevant information, is deficient in several neuropsychiatric conditions, including schizophrenia [1]. Sensorimotor gating can be operationally measured by prepulse inhibition (PPI) of the startle response [2]. Impaired PPI in rodents is used as a common endophenotype to model this basic attentional schizophrenia-like deficiency and to try to elucidate the mechanisms underlying schizophrenia symptoms. In this regard, findings from clinical and preclinical studies indicate that PPI is modulated by the cortico-striato-pallido-thalamic (CSPT) circuit [1,3]. Accordingly, we found a relationship between PPI differences and divergences in volume and activity of the medial prefrontal cortex (mPFC) in both intact inbred Roman and outbred rats [4]. Particularly, our data revealed that the schizophrenia-like Roman high-avoidance (RHA) rats show lower mPFC activity and PPI than the Roman low-avoidance (RLA) rats. Our findings raised the question of which type of neurons in the mPFC may be involved in the modulation of PPI. In this context, the GABA hypothesis of schizophrenia has been postulated to explain the etiology of cognitive symptoms [5], which are related to PPI dysfunction [6].

The GABA hypothesis of schizophrenia postulates that GABA-mediated cortical inhibition is dysfunctional in this disease, leading to excessive excitatory neural transmission to subcortical brain regions [5,7,8]. Particularly, it has been suggested that dysfunctional NMDA receptors in GABAergic interneurons do not activate these inhibitory neurons, and this leads to overactivation of glutamatergic projections [5,9]. In turn, this higher glutamatergic transmission would over-activate (i) the mesolimbic dopaminergic neurons, responsible for positive symptoms of schizophrenia; and (ii) the GABAergic neurons

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that project to the PFC, causing negative and cognitive symptoms [5]. This hypothesis is based on the evidence that schizophrenic patients exhibit poor gamma oscillation frequency in the PFC, a pattern of neuronal firing critical for cognitive abilities, such as attention and working memory [9–11]. Specifically, a subpopulation of GABA interneurons that expresses the calcium-binding protein parvalbumin (PV) seems to be essential to provide inhibitory inputs and to drive cortical gamma oscillations. Importantly, it has been recently demonstrated that excitatory synapses (measured by PSD-95) are selectively decreased on PV interneurons in the PFC of schizophrenic patients and this predicts the activity-dependent downregulation of PV [11]. In this sense, studies have shown reduced density of PV interneurons and/or expression of PV in both schizophrenic patients [12–14] and animal models of schizophrenia [2,15–17]. Regarding the role of PV interneurons in PPI, previous findings indicate that prenatal phencyclidine or lipopolysaccharide treatments reduce the density of PV-positive (PV+) cells and the c-Fos activity within the mPFC in parallel to PPI impairments [18,19]. Similarly, the PV knockout (PV–/–) mice show lower PPI than the PV+/+ control group [20].

The inbred RHA and RLA rats were bidirectionally selected for rapid vs. non-acquisition of the two-way active avoidance task, respectively. Interestingly, compared with their RLA counterparts, RHA rats exhibit reduced PPI, working memory, and latent inhibition. These behavioral phenotypes are accompanied by different neural abnormalities that indicate that the RHA rats might be a valid animal model to study the underlying mechanisms of schizophrenia-related symptoms [21].

In this study, we investigated, by triple fluorescence immunostaining, the degree of the colocalization of c-Fos (as indirect marker of activity) with PV interneurons and PSD-95 puncta on PV cell bodies in the mPFC of Roman rats after a PPI session. We hypothesize that the schizophrenia-like RHA rats, compared to the RLAs, would show fewer number of active PV interneurons and lower PSD-95 puncta on PV interneurons.

## 2. Materials and methods

We used 42 inbred male Roman rats (RHA = 21; RLA = 21) from our permanent colony at the Autonomous University of Barcelona. Rats were 2.5–3 months of age and weighted 220–290 g. They were housed in pairs in macrolon cages (50 × 25 × 14 cm) and maintained with food and water ad libitum, under a 12:12 light-dark cycle (lights on at 08:00 am) and controlled temperature (22 ± 2 °C) and humidity (50–60 %). All procedures were carried out in accordance with the Spanish Legislation (Royal Decree 53/2013, 1st February 2013) and the European regulation for "Protection of Animals used for Scientific Purposes" (2010/63/UE, 22 September 2010).

PPI was performed as previously described in [4]. In short, rats were individually located in an acrylic cylinder within a sound-attenuated box. The PPI session consisted of: (i) 5-min acclimation period; (ii) 10 pulse-alone trials (105 dB(A), SPL, 40 ms); (iii) 60 random trials of: 10 pulse-alone (used to calculate the %PPI), 10 prepulses of each intensity 65/70/75/80 dB(A, SPL, 20 ms) followed by pulse stimulus with an inter-stimulus interval of 100 ms, or non-stimulus trials (background noise of 55 dB). The %PPI for each prepulse intensity was obtained by applying the following formula: %PPI = [100 – (startle amplitude on prepulse trials/startle amplitude on pulse-alone trials x 100)]. The No-Pulse (NP), Prepulse-alone (Pre), and the Pulse-alone (Pulse) control groups for each strain underwent sessions of non-stimulus trials, prepulse-alone trials, and pulse-alone trials of the same duration as the PPI test. The distribution of groups was as follows: RHA-NP = 4; RHA-Pre = 4; RHA-Pulse = 5; RHA-PPI = 8; RLA-NP = 4; RLA-Pre = 4; RLA-Pulse = 6; RLA-PPI = 7.

Two hours after the described behavioral conditions, rats were euthanized with a lethal dose of pentobarbital and transcardially perfused with a solution of 0.1 M PBS followed by 3.7–4 % buffered formaldehyde. Removed brains were immersed in the same fixative at 4 °C for 2 h, washed twice and cryopreserved at 4 °C in 30 % sucrose buffered solution, until frozen in isopentane. Coronal 30-μm thick sections of the mPFC (Bregma: from 3.72 to 2.52 mm, infralimbic and prelimbic cortices) were cut in a cryostat (Leica CM3050S), collected free-floating, and stored at − 20 °C until immunostaining. After washes in PBS, antigen retrieval (citrate buffer pH 6) and blocking were performed (10 % normal horse serum (Sigma H0146). Slices were then incubated overnight at 4 °C with the three primary antibodies (goat anti-c-Fos IgG, Santa Cruz, SC52G, 1:500; mouse anti-PV, 1:2000, sigma; Rabbit anti-PSD-95, 1:1000, Abcam) diluted in "antibody diluent" (PBS-T with 1 % (w/v) BSA (Sigma A9647). After several washes in PBS-T (Tween 0.05 %), the slices were incubated with biotinylated horse anti-goat IgG (Vector Laboratories, 1:400) 40 min at RT. After washes in PBS-T, the slices were incubated with Alexa Flour 555 streptavidin, anti-mouse Alexa Flour 488, and anti-rabbit Alexa Flour 647 (ThermoFisher Scientific, 1:750 in antibody diluent, 45 min at RT). Finally, counterstaining (Hoechst, 1:10,000) was performed, and the slices were mounted on slides, air dried and coverslipped with aqueous medium.

Brain images were taken on a confocal microscope (Leica SP5) using a 63x/1.50 NA SC oil immersion objective by an experimenter blinded to treatment condition. For each animal, in three sections of the mPFC, fifteen image stacks (512 × 512; 0.7 μm) were randomly selected. We used the IMARIS 9.5 software to automatically identify and count the number of c-Fos and PV nuclei and PSD-95 puncta per $mm^2$ and calculate the average for each animal. Based on the ability of antibodies to penetrate tissue, we obtained a representative image of objects that were in the middle of the z-planes (see a representative example in Fig. 1). No group differences were observed in the mean volume of tissue sampled.

Colocalization of c-Fos and PV cell bodies was calculated to determine the density of active PV interneurons. The percentage of PV interneurons colocalized with c-Fos (%PV+/c-Fos) was determined by the following formula: PV/c-Fos density = [number of "PV+c-Fos+" cells /"PV+ total" cells x 100]. The number of PSD-95 puncta per surface area of "PV+ total" or "PV+c-Fos+" cells was calculated to determine the density of excitatory synapses on PV interneurons or active PV interneurons, respectively.

All the analyses were performed using the SPSS software. Student's *t*-test was used to test for significant PPI differences between RHA and RLA rats. ANOVA ('2 strains x 4 conditions') was used to explore differences in the neural markers and behavioral conditions between the RHA and RLA rats. Significance level was set at $p < 0.05$.

## 3. Results

Behavioral data showed lower PPI in the RHA rats than RLAs, but no differences in startle response (Table 1).

In relation to neuronal activity, ANOVA revealed 'Strain' ($F_{(1,34)}$= 23.711; $p$ = <0.001), 'Condition' ($F_{(3,34)}$= 3.863; $p$ = 0.018), and 'Strain x Condition' ($F_{(3,34)}$= 2.985; $p$ = 0.045) effects in c-Fos activity in the mPFC. Importantly, Duncan's post hoc test confirmed that the RLA rats under the PPI conditions showed higher c-Fos activity than the NP, Pre, and Pulse RLA groups and all the RHA groups, while there were no differences among RHA groups (Fig. 2b).

Regarding PV interneurons, 2 × 4 ANOVA revealed a significant 'Strain' effect ($F_{(1,34)}$ = 15.891; $p$ = <0.001; Fig. 2a), as the RLA rats showed a higher number of PV+ cells in the mPFC than the RHA rats, both in cell bodies and surface area. There were no 'Condition' ($F_{(3,34)}$ = 0.256; $p$ = 0.857) or 'Strain × Condition' ($F_{(3,34)}$ = 1.172; $p$ = 0.335) effects.

On the other hand, concerning the percentage of c-Fos positive PV interneurons, 2 × 4 ANOVA showed a significant 'Strain' effect ($F_{(1,34)}$ = 4.864; $p$ = 0.034), as it was globally higher in the RLA than in the RHA rats, and a "Strain x Condition" effect ($F_{(3,34)}$ = 2.894; $p$ = 0.049). Post-hoc Duncan's test confirmed that the RLA under the PPI condition showed higher percentage of active PV interneurons than the RLA control groups and the RHA groups ($p < 0.05$; Fig. 2d). In fact, the RHA-

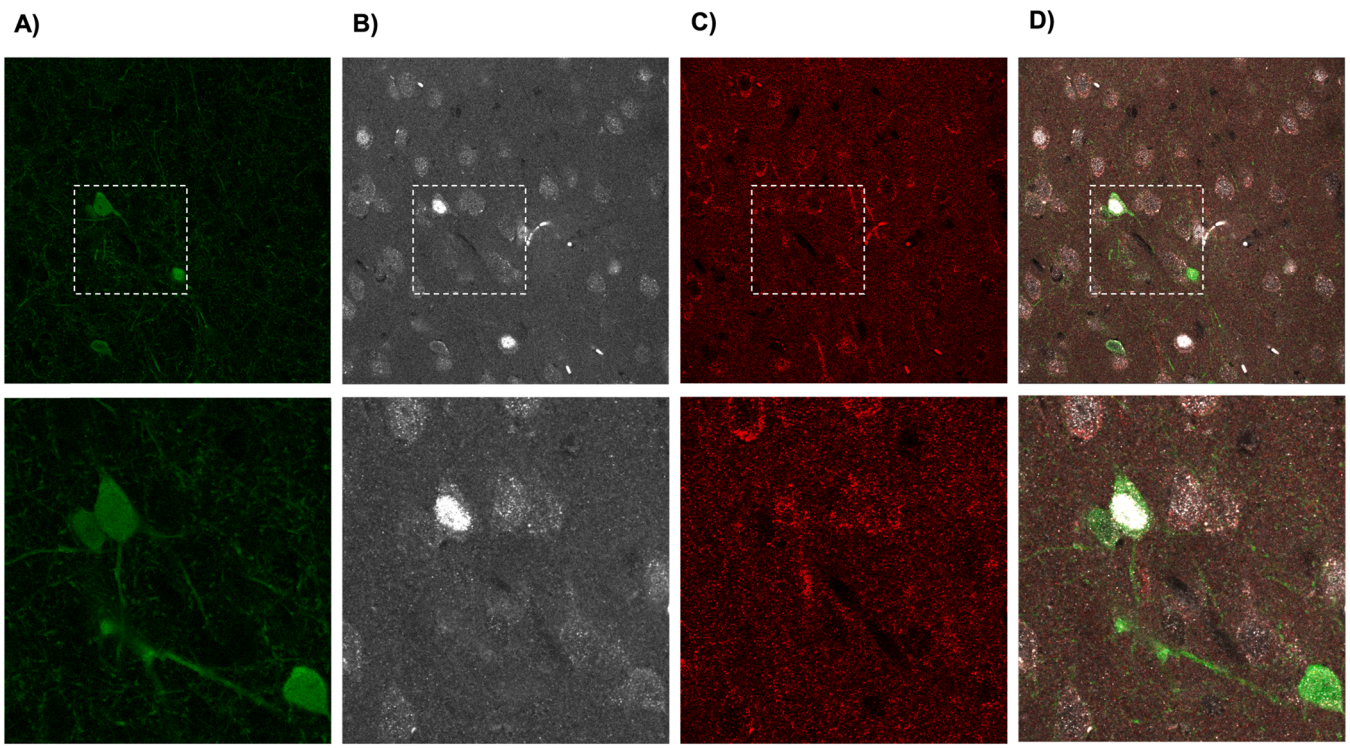


**Fig. 1.** Triple immunofluorescence staining for parvalbumin (PV)-containing interneurons, c-Fos expression and PSD-95 puncta. Representative images of PV (A), c-Fos (B), PSD-95 puncta (C) markers and merged images (D).

**Table 1**
Mean ± SEM of startle response amplitude and prepulse inhibition in RHA and RLA rats. Student's t-test showed Strain effects on "PPI 65_70dB" (average of the two lower prepulse intensities) [$t_{(1,13)}$= 2.885; p = 0.013] and "PPI Total" (average of all prepulse intensities, i.e. 65, 70, 75, 80 dB) [$t_{(1,13)}$= 2.395; p = 0.032]. No differences were found in Startle response (average of pulse trials to calculate PPI) [$t_{(1,13)}$= 0.776; p = 0.452]. *, significant difference vs the corresponding RHA group.

| | RHA-PPI (n = 8) | RLA-PPI (n = 7) |
|---|---|---|
| Startle response | 922.1 ± 174.1 | 1190.7 ± 199.8 |
| PPI 65_70dB | 43.9 ± 7.2 | 67.6 ± 3.0* |
| PPI Total | 57.1 ± 6.1 | 73.8 ± 2.5* |

PPI rats, compared to their RLA-PPI counterparts, exhibit an approximately 60 % reduced activation of PV interneurons.

Finally, regarding PSD-95, no significant effects were observed in either total number of PSD-95 puncta or PSD-95 puncta on PV+ cells (Fig. 2c and e, respectively; all $p > 0.498$). However, we found a 'Strain' effect in the density of PSD-95 puncta on active PV+ cells (PSD-95 puncta on "PV+c-Fos+" cells; $F_{(1,34)} = 6.447$; $p = 0.016$), as it was globally higher in RLA rats than in RHAs (Duncan's post hoc test, $p < 0.05$; Fig. 2f). No 'Condition' ($F_{(3,34)} = 0.227$; $p = 0.841$) or 'Strain × Condition' ($F_{(3,34)} = 0.159$; $p = 0.923$) effects were found in the density of PSD-95 puncta on active PV+ cells.

## 4. Discussion

This study aimed to elucidate specific mechanisms associated with reduced mPFC activity during PPI in the RHA rats compared to the RLAs. Our results indicate that it might be explained by differences in the activation of PV interneurons. Specifically, we show that the RHA rats display both lower PPI and activation of PV interneurons than the RLAs.

Our result showing a relationship between reduced activation of PV interneurons and low PPI agrees with several studies reporting reduced number of PV interneurons in schizophrenia [12–14] and animal models of neuropsychiatric disorders [2,15–17]. For example, prenatal and postnatal neurodevelopmental models of schizophrenia have shown impaired PPI associated to reduced density of PV interneurons and c-Fos activity in the PFC after PPI [18,19], while loss of PV gene involves impaired PPI [20]. In contrast, other animal models of schizophrenia, such as maternal immune activation with polyI:C, report no changes in PV interneurons, but differences in perineuronal nets surrounding PV interneurons in the medial prelimbic cortex [22]. Regarding PV interneurons density, we have shown that the schizophrenia-like RHA rats exhibit lower density of inhibitory PV interneurons in the mPFC than the RLAs. However, as noted in Refs. [16,18], we may consider that the use of fluorescent immunohistochemistry may not allow us to determine whether the RHA rats had lower PV expression (below the detection limit) rather than loss of PV interneurons, as it happens in the NR1-deficient mice model of schizophrenia [23]. Indeed, in a previous study with the Roman rats using the more sensitive HRP-immunocytochemistry and stereology, we found no between-strain differences in PV numbers in the frontal cortex in basal conditions [24]. Nevertheless, the possible differences in PV expression between the Roman rats are in line with differences observed in PV interneurons activation, as lower PV expression would also indicate lower activity [11]. This is consistent with previous reports showing that schizophrenic patients display lower GAD67 expression in PV interneurons [25,26], as well as reduced density of PV interneurons [2,13,14]. In this sense, a reduced activation of PV interneurons could drive to the disinhibition of pyramidal neurons that causes increased mesolimbic dopamine and schizophrenia-like symptoms in the RHA rats [21]. Accordingly, exogenous oxytocin administration, which shows an inhibitory profile on GABA/Glutamate function, attenuates natural PPI deficits in the RHA rats [27].

On the other hand, we did not find differences either between strains or the PPI groups in PSD-95 puncta density, which contrasts with a previous study in humans reporting an 18 % reduction in mean density of PSD-95 puncta on PV+ interneurons in schizophrenic patients [11].

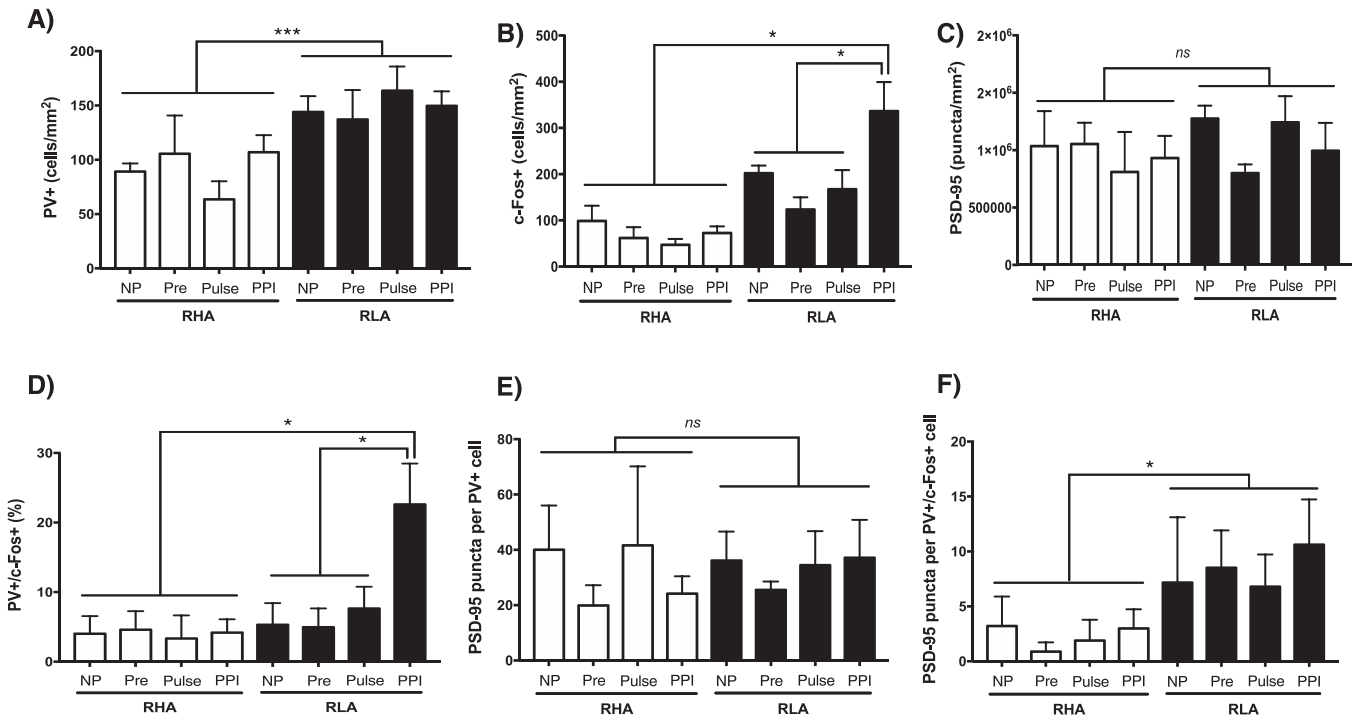


**Fig. 2.** Reduced PPI in Roman rats is related to decreased activation of parvalbumin-positive (PV+) cells in the medial prefrontal cortex. A) The RHA rats show globally lower PV+ density than the RLAs. B) The RLA rats in the PPI condition showed higher c-Fos activity in the mPFC than the RLA control groups (NP, no-pulse; Pre, prepulse-alone; Pulse, pulse-alone) and all the RHA groups. C) No differences in the density of PSD-95 puncta were observed. D) The RLA rats in the PPI condition show a higher percentage of active PV+ interneurons than the RLA control groups (NP, no-pulse; Pre, prepulse-alone; Pulse, pulse-alone) and all the RHA groups. E) No differences in the density of PSD-95 puncta on PV+ cells were observed. F) The RHA rats show globally lower density of PSD-95 puncta on active PV+ interneurons than the RLAs. Values are mean ± SEM. See "n"/groups in Methods. *$p < 0.05$; ***$p < 0.001$; *ns*, non-significant (Duncan's multiple range test).

However, interestingly, we found strain differences in the mean density of PSD95 puncta on "PV+c-Fos+" interneurons, as the schizophrenia-like RHA rats showed globally lower PSD-95 density on active PV+ cells than the RLA strain. Even though PSD-95 seems not to be related to PPI performance, this finding is consistent with the idea that the excitatory drive plays a role in the activity of PV interneurons. For future studies, it would be interesting to analyze other GABAergic interneurons or glutamatergic neurons, as well as the broad CSPT circuit, to determine the specificity of the present findings.

Our data indicate that the lower neuronal activity in the mPFC during PPI, showed by the RHA rats relative to the RLAs, might be explained by differences in PV interneurons activation. This result points to reduced cortical inhibition as a likely candidate to explain the schizophrenia-like features observed in the RHA rats and supports the role of impaired cortical inhibition in schizophrenia. Moreover, our findings could also apply to other neuropsychiatric conditions, such as obsessive compulsive disorder and Gilles de la Tourette's syndrome, which are accompanied by impaired PPI [1].

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## Conflict of interest

The authors declare no competing interests.

## Data Availability

The authors do not have permission to share data.

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