Schizophrenia Bulletin vol. 50 no. 1 pp. 210–223, 2024
https://doi.org/10.1093/schbul/sbad123
Advance Access publication August 16, 2023

Prefrontal and Hippocampal Parvalbumin Interneurons in Animal Models for Schizophrenia: A Systematic Review and Meta-analysis

Thamyris Santos-Silva[1,4], Débora dos Santos Fabris[2,4], Cilene Lino de Oliveira[3], Francisco S. Guimarães[1], and Felipe V. Gomes[*,1]

[1]Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; [2]Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; [3]Department of Physiological Sciences, Center of Biological Sciences, University of Santa Catarina, Florianópolis, Brazil

[4]Joint first authors.

[*]To whom correspondence should be addressed; Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, 3900, Bandeirantes Avenue, Ribeirão Preto, São Paulo 14040-900, Brazil; tel: +55 (16) 3315-3326; fax: +55 (16) 3315-0220, e-mail: gomesfv@usp.br

***Background*: Consistent with postmortem findings in patients, most animal models for schizophrenia (SCZ) present abnormal levels of parvalbumin (PV), a marker of fast-spiking GABAergic interneurons, in the prefrontal cortex (PFC) and hippocampus (HIP). However, there are discrepancies in the literature. PV reductions lead to a functional loss of PV interneurons, which is proposed to underly SCZ symptoms. Given its complex etiology, different categories of animal models have been developed to study SCZ, which may distinctly impact PV levels in rodent brain areas. *Study Design*: We performed a quantitative meta-analysis on PV-positive cell number/density and expression levels in the PFC and HIP of animal models for SCZ based on pharmacological, neurodevelopmental, and genetic manipulations. *Results*: Our results confirmed that PV levels are significantly reduced in the PFC and HIP regardless of the animal model. By categorizing into subgroups, we found that all pharmacological models based on NMDA receptor antagonism decreased PV-positive cell number/density or PV expression levels in both brain areas examined. In neurodevelopmental models, abnormal PV levels were confirmed in both brain areas in maternal immune activation models and HIP of the methylazoxymethanol acetate model. In genetic models, negative effects were found in neuregulin 1 and ERBB4 mutant mice in both brain regions and the PFC of dysbindin mutant mice. Regarding sex differences, male rodents exhibited PV reductions in both brain regions only in pharmacological models, while few studies have been conducted in females. *Conclusion*: Overall, our findings support deficits in prefrontal and hippocampal PV interneurons in animal models for SCZ.**

Key words: excitatory-inhibitory balance/psychosis/psychiatry/GABA/preclinical research/model organisms

Introduction

Preclinical and clinical studies have indicated that changes in fast-spiking GABAergic interneurons containing the calcium-binding protein parvalbumin (PV) are common in schizophrenia (SCZ).[1,2] Reductions in the number and density of PV interneurons in the prefrontal cortex (PFC) and hippocampus (HIP) have been found in the postmortem brain of SCZ individuals.[3–8] Similar changes have been reported in animal models for SCZ.[9]

PV interneurons are critical for the rhythmic activity of the PFC and HIP, given their essential role in maintaining a local excitatory-inhibitory (E/I) balance by synchronizing the firing state of pyramidal glutamatergic neurons.[10–13] Dysregulation in the E/I balance is proposed to underline the main SCZ symptoms, including positive, negative, and cognitive. Abnormal PV interneuron function in the PFC has been associated with cognitive impairments and negative symptoms.[14–16] In addition, the striatal hyperdopaminergic state, which has long been implicated in psychotic symptoms, could result from a functional loss of hippocampal PV interneurons.[14,17,18]

Animal models are valuable tools to test new drug targets and investigate the neurobiological basis of SCZ by mimicking genetic and environmental risk factors for the disorder.[19–21] The main SCZ models currently employed involve pharmacological interventions to mimic the striatal hyperdopaminergic state (using drugs such as amphetamine) or hypofunction of glutamate NMDA receptors (using NMDA receptor antagonists, such as ketamine,

phencyclidine, or MK-801), neurodevelopmental disruption to mimic the exposure to environmental factors contributing to SCZ during the prenatal and early postnatal period, and alterations in single risk genes implicated in the disease. Prefrontal and hippocampal PV changes have been described in most of these models. However, despite the numerous studies investigating these changes, they have yet to be systematically reviewed. Furthermore, the impact of these models on PV changes and their magnitude of effect according to brain regions (PFC and/or HIP) remain to be quantitatively explored. Here, we broadly categorized animal models used in SCZ research into pharmacological, neurodevelopmental, and genetic models. Next, we systematically reviewed and performed a meta-analysis of studies investigating PV changes through immunohistochemistry/immunofluorescence and/or western blot (WB) methods. Whenever possible, we presented a detailed subanalysis comparing the timing of drug intervention in pharmacological models, the age at which PV was evaluated, species (rats vs mice) and sex.

Methods

This review followed the preferred reporting items for systematic reviews and meta-analyses.[22] All analytic decisions were taken beforehand to reduce the risk of bias in our analysis. Protocol was preregistered at the PROSPERO platform (CRD42020214421, Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020214421).

Search Strategy

Articles were searched in relevant web databases (PubMed, Scopus, and Web of Science) that were arbitrarily chosen considering their extensive collection of international publishers in basic biomedicine. The descriptors (search terms) included the following combinations: (Parvalbumin AND [schizop * OR psychosis]). The included references were analyzed using the Rayyan application to assist in the initial screening.[23] Articles published until April 21, 2020, were used as inclusion criteria.

Study Selection

Two independent reviewers applied eligibility criteria; a third reviewer solved discrepancies. The first phase of study selection was a prescreening based on the title and abstract, followed by the appraisal of the full text. The review included only original articles published in English that evaluated the expression levels of PV protein by WB and/or total PV-positive cells number and/or density (PV-positive cells per mm^2 or mm^3) by immunohistochemistry/immunofluorescence in the PFC and HIP, following 3 categories of SCZ animal models: (1) pharmacological models based on the administration of NMDA receptor antagonists—MK-801, ketamine, phencyclidine (PCP); (2) neurodevelopmental models—methylazoxymethanol (MAM), maternal immune activation (using poly I:C or lipopolysaccharide [LPS)]); neonatal stress, social isolation, adolescent stress, neonatal lesion (ventral HIP neonatal lesion); (3) genetic models included animals with single mutations in disrupted-in-schizophrenia-1 (DISC1), dystrobrevin-binding protein 1 (DTNBP1), neuregulin (NGR1) and ErbB4, and NMDA receptor subunits genes. Although there are other genetic models related to SCZ (22q11.2 deletion, reelin, and Gclm knockout), they were not included given the few numbers or even lack of studies evaluating PV in the selected brain regions.

Articles that reported data from the medial PFC or its prelimbic portion (analogous to the Brodmann Area 32 in humans) and the dorsal HIP (analogous to the posterior HIP in humans) or its CA3 subregion were included. Since few studies have evaluated other medial PFC (such as its infralimbic portion), dorsal HIP subregions (such as the dentate gyrus and CA1), and the ventral HIP, they were not included. Exclusion criteria included: editorials, comments and letters, abstracts, book and magazine chapters, dissertations and thesis, articles written in languages other than English, systematic and meta-analysis reviews, case studies, clinical studies, human postmortem studies, studies in vitro, and electrophysiological studies without evaluation of expression or the number of PV interneurons. Full texts without appropriate control groups, outcome measures of PV levels, brain regions/subregions, intervention, or exposure protocol without dose or time of administration/evaluation were excluded. In the absence or inability to extract data for meta-analysis (eg, group size, mean, standard deviation, standard error of mean, or nonparametric test), the study was excluded during the second phase of data extraction.

Data Extraction

Two independent reviewers extracted data from text, table, or graphs (using a digital screen ruler or contacting authors), and a third reviewer resolved the discrepancies. Agreement between reviewers was assessed by using the "comparing columns" tool of Excel (qualitative data). For a qualitative summary of included studies, bibliographic information, population, intervention, comparison, and the qualitative and quantitative aspects of the outcomes were extracted. Qualitative data were extracted from each study to describe animal model characteristics (species, strain, sex, phenotype induced by an intervention or exposure, or a transgenic construct), intervention characteristics (type of intervention or exposure, type of transgenic construct, lifetime period of intervention, lifetime period of evaluation, technical procedures, anatomic region (PFC, dorsal and ventral HIP), control characteristics (type of control, technical procedures), outcome characteristics (type of PV immunoassay/molecular

biology assay, behavioral tests, scale of measure, timing of measure), and risk of bias assessment (RoB Syrcle tool[24]). Quantitative data (mean, standard error, or standard deviation of the mean, sample size per group, and number of comparisons among groups) was extracted to describe characteristics of the study design, the estimate of effect sizes, and meta-analysis.

Meta-analyses

Random effects model meta-analysis was used to calculate the combined effect size (CES, Hedges' *g*), publication bias, and proportion of heterogeneity (I^2) with relevant data extracted from the included studies (mean, standard deviation, and sample sizes). When studies failed to report the precise sample sizes, the mean of the sample size reported in the calculations was used. Magnitudes of CES were interpreted according to the following arbitrary definitions following previous studies: "very small" (0.01–0.2), "small" (0.2–0.5), "medium" (0.5–0.8), "large" (0.8–1.2), "very large" (1.2–2), and "huge" (≥2).[25] CES was considered "statistically significant" when a 95% confidence interval spares the null effect and "inconclusive" when a 95% confidence interval overlaps the null.[26] The potential publication bias was estimated by Funnel plot and Trim-and-Fill. The proportion of heterogeneity (I^2) was interpreted as the following arbitrary criteria: "very low" (0%–25%), "low" (25%–50%), "moderate" (50%–75%), and "high" (≥75%).[27] A pairwise meta-analysis (control versus animal model) was made *per* type of animal model (pharmacological, neurodevelopmental, or genetic models) *per* brain region (PFC or HIP). Data from the included studies were also stratified to subgroups meta-analysis based on: (1) subtype of intervention, (2) age of intervention, (3) age of PV evaluation, (4) species, and (5) sex.

Results

Characteristics of the Studies Included in the Meta-analysis

The bibliographic searches returned a total of 2256 references. No additional articles were included. Duplicate results among databases resulted in the exclusion of 1112 studies. The eligibility criteria excluded 1021 articles, including 90 references for the full-screening phase (figure 1). After screening, 90 articles were considered eligible for the meta-analysis (figure 1; also see reference list in the Supplementary material for details).

Most articles evaluated PV changes (eg, considering all methods together) in pharmacological ($k = 39$) and neurodevelopmental models ($k = 35$), whereas 15 studies were performed in genetic models (Supplementary table 1). In addition, 1 article employed both pharmacological and neurodevelopmental models independently. Among the pharmacological models, 18 and 10 studies explored, respectively, PFC and HIP, while 12 of them evaluated both brain areas (Supplementary table 1.1). In models based on neurodevelopmental disruption, 6 studies evaluated PV changes in the HIP, 14 investigated the PFC, and 15 assessed both brain areas (Supplementary table 1.2). Considering the genetic models, 7 and 6 studies included prefrontal and hippocampal analyses, respectively, and 2 explored both regions (Supplementary table 1.3). Most studies reported reductions in PV-positive cell number and/or PV expression levels. However, 5 studies reported increased PV levels, in which 2 applied pharmacological manipulation. Chronic ketamine treatment during adulthood enhanced PV-positive cell numbers in the HIP,[28] and neonatal ketamine treatment increased PV protein levels in the PFC.[29] Other 2 studies described that maternal immune activation with LPS augmented prefrontal and hippocampal PV density.[30,31] Transgenic mice with DISC1-L100P point mutation had enhanced hippocampal PV-positive cell number.[32] Notably, 22 studies reported no changes in PV levels, which were distributed among pharmacological (8), neurodevelopmental (9), and genetic (5) models. The most employed methodological approach was immunohistochemistry or immunofluorescence (75). Forty-one studies measured total PV-positive cell number and 34 PV density. WB was used in 12 of the included studies, and only 4 employed both methods to quantify PV interneurons.

PV Changes in Animal Models to Study SCZ

Considering all studies included in the review (eg, all methods together), the CES for PV was negative, large, and significant in the PFC and HIP (figures 2A and B, Supplementary table 2). Similar findings were observed after stratifying the studies into pharmacological, neurodevelopmental, and genetic models (figures 2C and D). Still, the magnitude of effect size varied among models and brain areas from medium to very large (figures 2C and D). The I^2 test revealed a moderate proportion of heterogeneity, suggesting the presence of subgroups across each animal model category. On the other hand, the proportion of heterogeneity was considered low in hippocampal analyses performed in animals from neurodevelopmental models (Supplementary table 2). Therefore, we investigated PV changes in pharmacological (table 1), neurodevelopmental (table 2), and genetic models (table 3) stratified in subgroups whenever possible by comparing the model employed, age of drug intervention (neonatal, prepubertal, adolescence, and adulthood), period of PV evaluation, species, and sex.

Prefrontal and Hippocampal PV Changes Stratified into Subgroups of Studies

Pharmacological Models. The CES estimated in the studies using pharmacological models were negative and significant in both brain regions for most subgroups, including

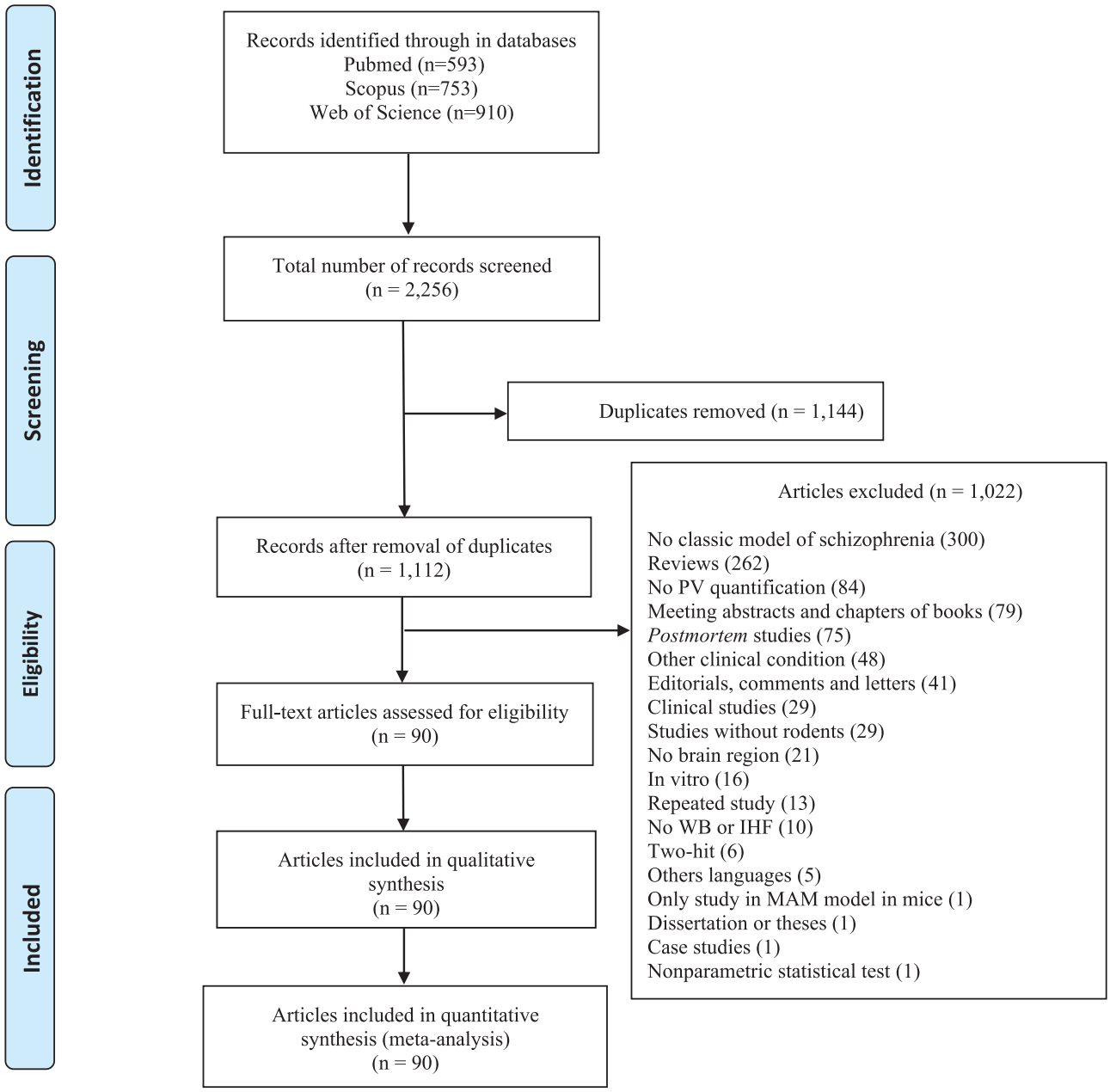

Fig. 1. PRISMA flowchart showing the inclusion of studies for the meta-analysis.

"all models" (table 1). In the HIP, except for the inconclusive estimates of CES in the "all ages of drug exposition," "all ages of PV evaluation," and "both species" subgroups, the CES were negative and significant. A similar pattern of results was observed in the PFC, except for the inconclusive estimate of CES in the "all sexes" subgroup.

In the conclusive estimates of the CES, the magnitude varied across types of models and brain regions. CES in the "MK-801" subgroup was defined as huge in the PFC and medium in the HIP, while "Ketamine" and "PCP" subgroups were classified as large and very large, respectively, in both brain areas. By comparing the time of drug administration subgroups, we found that CES was negative and significant in most evaluated periods and brain regions, except for analysis in the HIP of the "Adolescence" subgroup. In addition, CES was considered very large in the PFC of all-time drug intervention subgroups. A very large CES was identified in animals exposed to pharmacological models during adulthood in the HIP. CES was considered large and small in the "Neonatal" and "Prepubertal" subgroups, respectively. Regarding the time of PV evaluation, all CES were negative and significant, except for the "Adolescence" subgroup in the HIP. In the "Adolescence" subgroup, our analysis revealed a huge CES in the PFC, which was very large in both brain regions of "Adulthood" subgroups.

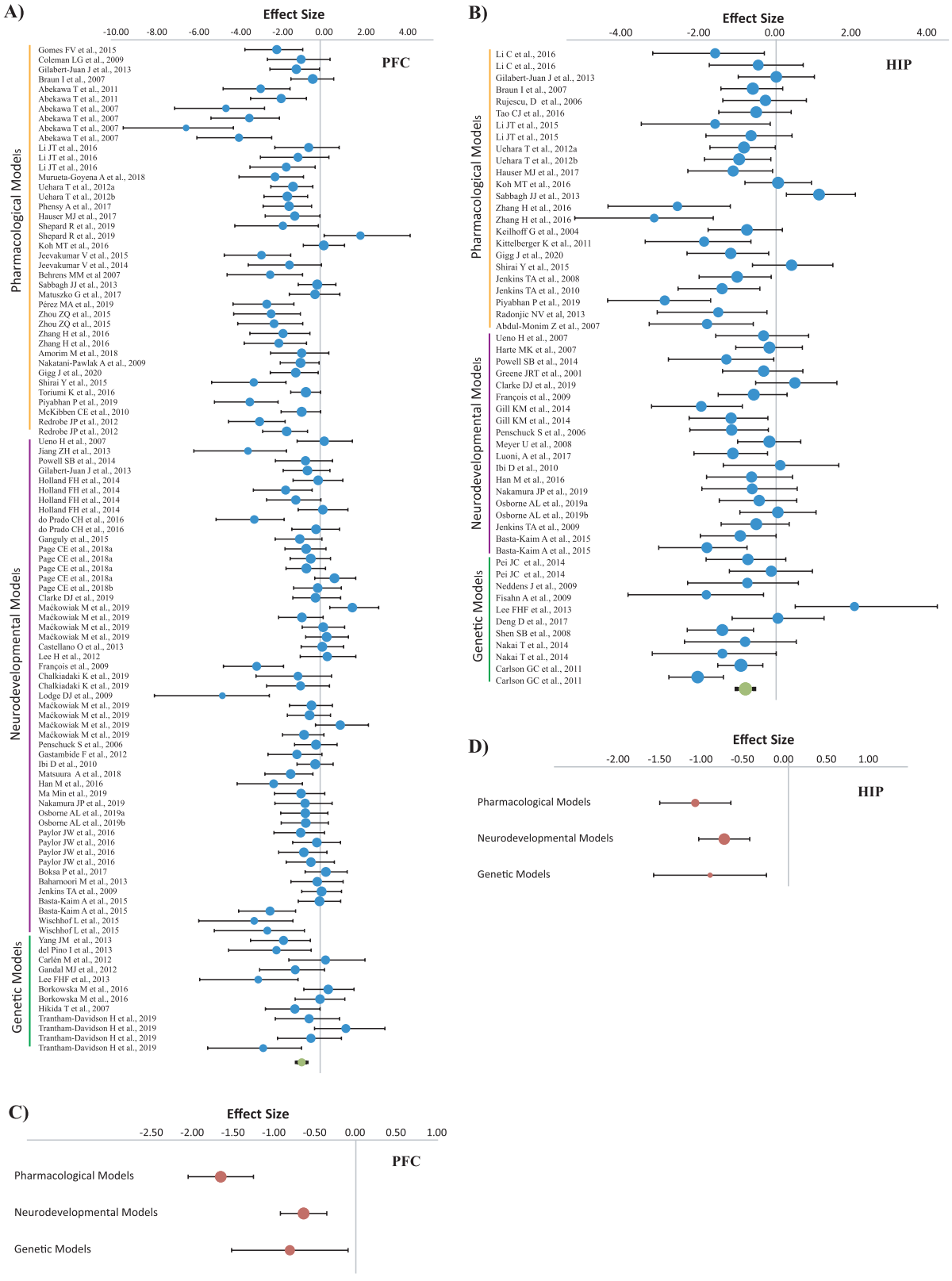

Fig. 2. Forest plots of PV interneuron changes in animal models to study SCZ. Meta-analysis of studies measuring PV interneurons cell number, density, and protein expression levels in the (**A**) PFC and (**B**) HIP. (**C** and **D**) Meta-analysis of selected studies stratified into 3 categories (pharmacological, neurodevelopmental, and genetic models) according to brain areas.

Table 1. CES (Hedges' *g*) of PV Changes in Pharmacological SCZ Models Stratified into Subgroups of Studies

	PFC						HIP					
	CES	95% CLL	95% CLU	*N* analysis/ samples	I^2	*P*-value	CES	95% CLL	95% CLU	*N* analysis/ samples	I^2	*P*-value
All models	−1.61	−3.04	−0.18	40/577	71.5%	0.15	−1.05	−1.47	−0.62	24/352	69.2%	0.43
MK-801	−2.02	−2.74	−1.29	16	71.9%		−0.69	−1.02	−0.37	10	0.0%	
Ketamine	−1.28	−1.88	−0.69	16	71.2%		−1.15	−2.18	−0.11	7	85.6%	
PCP	−1.28	−1.98	−0.59	8	65.0%		−1.43	−2.25	−0.62	7	70.5%	
All ages of drug exposition	−1.50	−3.53	0.52	40/577	71.7%	0.22	−0.61	−1.80	0.59	24/352	69.2%	0.11
Prenatal	−1.67	−2.93	−0.42	3	76.1%		NA	NA	NA	NA	NA	
Neonatal	−1.80	−2.50	−1.10	19	74.8%		−0.88	−1.24	−0.52	9	2.4%	
Prepubertal	NA	NA	NA	NA	NA		−0.46	−0.73	−0.18	2	0.0%	
Adolescence	−1.29	−2.16	−0.43	7	70.4%		0.22	−0.17	0.60	2	0.0%	
Adulthood	−1.62	−2.26	−0.99	11	70.1%		−1.57	−2.35	−0.80	11	78.8%	
All ages of PV evaluation	−1.59	−3.62	0.43	39/565	72.2%	0.19	−0.93	−3.01	1.14	23/340	67.8%	0.35
Adolescence	−2.26	−3.81	−0.71	7	83.7%		−0.72	−1.50	0.05	3	21.3%	
Adulthood	−1.44	−1.84	−1.05	32	68.0%		−1.02	−1.49	−0.54	20	71.1%	
Both species	−1.53	−3.55	0.44	40/577	71.1%	0.11	−0.95	−2.41	0.51	24/352	69.2%	0.32
Mice	−1.24	−1.87	−0.61	14	69.1%		−0.66	−1.34	0.03	8	57.6%	
Rats	−1.74	−2.24	−1.23	26	72.1%		−1.18	−1.70	−0.66	16	72.3%	
All sexes	−1.50	−2.93	−0.07	40/577	71.1%	0.28	−1.24	−3.30	0.83	24/352	69.2%	0.32
Male	−1.45	−1.83	−1.07	35	67.1%		−1.00	−1.46	−0.54	22	70.5%	
Female	−3.66	−6.69	−0.63	3	89.6%		−1.57	−2.25	−0.89	2	0.0%	
Male and female	−1.30	−2.76	0.17	2	0.0%		NA	NA	NA	NA	NA	

CES = combined effect size; 95% CLL = 95% confidence interval lower limit; 95% CLU = 95% confidence interval upper limit; N = number; NA = not available.

Across rodent species, the CES of the "Mice" and "Rats" subgroups were significant in the PFC, while only the CES of the "Rats" subgroup was significant in the HIP. When we stratified the subgroups according to sex, the CES of studies using "Male" or "Female" were negative and significant in the PFC and HIP, suggesting that pharmacological models impact PV levels in both sexes. Specifically, we found that "Female" subgroups exhibit huge and very large CES in the PFC and HIP, respectively, while in "Male" subgroups, it was very large and large. In addition, the CES of studies that evaluated prefrontal PV changes considering the "Male and Female" subgroup were inconclusive in the PFC and unavailable in the HIP studies.

Neurodevelopmental Models . The CES estimated in the neurodevelopmental model studies was negative and significant in both brain regions for most subgroups (table 2, Supplementary table 2). Although large and negative, the CES in the subgroups "all models," "both species," and "all sexes" were inconclusive in both brain regions (table 2). The CES in the subgroup "all ages of PV evaluation" was large, significant in the HIP, and inconclusive in the PFC.

Among the significant estimates, a large CES was found in the "Neonatal Stress" and "Poly I:C" subgroups in the PFC. In the HIP, CES was significant for "MAM," "Poly I:C," and "LPS" subgroups, and their magnitude varied from medium to very large. These findings confirmed PV changes after environmental insults were applied in perinatal and neonatal periods. Due to the exclusion criteria, data from studies regarding "Neonatal Stress," "Adolescent Stress," and "Neonatal lesion" subgroups in the HIP were not included in the meta-analysis.

By stratifying data according to the time of PV evaluation, subgroups showed that the CES of the "Adulthood" subgroup was negative and significant in the PFC and HIP, in which both magnitudes of effect size were large. Heterogeneity was moderate in the PFC and very low in the HIP. Moreover, CES was not significant for the "Prepubertal" and "Adolescence" subgroups in the PFC and unavailable for the HIP.

Considering findings stratified by species, CES was significantly negative for the "Mice" and "Rats" subgroups in the PFC, with a medium effect size for both. In contrast, significant CES was observed only in the "Rats" subgroup of HIP analysis. Our analysis of PV changes according to sex showed that CES in all sex subgroups was considered negative and significant, except for the "female" subgroup in the HIP. The magnitude of effect size was diverse from medium to large.

Genetic Models . The CES estimated in the studies using genetic models were negative, varying in magnitude and significance from subgroup to subgroup (table

Table 2. CES (Hedges' *g*) of PV Changes in Neurodevelopmental SCZ Models Stratified into Subgroups of Studies

	PFC						HIP					
	CES	95% CLL	95% CLU	*N* analysis/ samples	I^2	*P*-value	CES	95% CLL	95% CLU	*N* analysis/ samples	I^2	*P*-value
All models	−0.60	−1.42	0.22	51/709	63.5%	0.13	−0.86	−2.08	0.36	19/275	30.7%	0.17
MAM	−0.70	−1.47	0.07	9	63.2%		−1.52	−2.06	−0.97	3	0.0%	
Poly I:C	−0.74	−1.05	−0.44	11	0.0%		−0.50	−0.81	−0.10	7	0.0%	
LPS	−0.94	−2.01	0.13	7	78.3%		−1.13	−1.94	−0.32	3	44.3%	
Neonatal stress	−0.86	−1.60	−0.11	7	63.2%		NA	NA	NA	NA	NA	
Social isolation	−0.94	−2.40	0.51	4	72.0%		−0.48	−0.98	0.02	4	0.0%	
Adolescent stress	−0.05	−0.50	0.40	10	52.6%		NA	NA	NA	1	NA	
Neonatal lesion	−0.82	−2.99	1.35	3	88.7%		NA	NA	NA	1	NA	
All ages of PV evaluation	−0.60	−2.02	0.82	50/696	64.1%	0.11	−0.69	−0.95	−0.43	17/246	9.0%	0.45
Prepubertal	−0.43	−1.11	0.25	3	10.9%		NA	NA	NA	NA	NA	
Adolescence	−0.45	−0.98	0.09	14	70.58%		NA	NA	NA	NA	NA	
Adulthood	−0.72	−1.09	−0.36	32	64.2%		−0.69	−0.95	−0.43	17	9.0%	
Both species	−0.63	−2.64	1.38	51/709	63.5%	0.11	−0.64	−2.74	1.46	19/275	37.3%	0.32
Mice	−0.66	−1.10	−0.22	19	52.5%		−0.38	−0.82	0.07	7	18.9%	
Rats	−0.61	−0.97	−0.26	32	67.4%		−0.88	−1.26	−0.50	12	38.3%	
All sexes	−0.63	−2.05	0.79	51/709	63.5%	0.13	−0.58	−2.06	0.91	19/275	37.3%	0.55
Male	−0.60	−0.96	−0.24	34	66.9%		−0.80	−1.20	−0.39	11	42.7%	
Female	−0.75	−1.42	−0.07	9	69.9%		−0.84	−1.93	0.26	4	67.6%	
Male and female	−0.60	−1.18	−0.02	8	45.9%		−0.35	−0.68	−0.03	4	0.0%	

CES = combined effect size; 95% CLL = 95% confidence interval lower limit; 95% CLU = 95% confidence interval upper limit; N = number; NA = not available.

3, Supplementary table 2). Effect size magnitudes were very large and medium in the PFC and HIP, respectively. Indeed, most of the CES estimates were inconclusive, except for the subgroups "neuregulin/ErBb4" in both regions, "adulthood" and "males" in the PFC, "dysbindin" and "neuregulin/ErBb4" in the HIP (table 3). CES in the "NGR1/ErBb4" subgroup was negative and significant in both brain areas. Moreover, CES for the "dysbindin" subgroup was significant and very large in the HIP. Regarding the age of PV evaluation, only CES of the "Adulthood" subgroup in the PFC was considered significant, along with a negative and large effect size. In addition, our analysis revealed that CES in the "Male" subgroup was the only significant in the PFC, which was considered large. Notably, no included genetic studies assessed PV changes in "Female" subgroups in the PFC or HIP.

Publication Bias and Methodological Quality of the Studies

Estimating potential publication bias, funnel plot and Trim-and-Fill proposed 2 studies missing to adjust CES of analyses conducted for the PFC, with a modest change to a value of −1.00 (−1.26, −0.74), but still negative and without changing the large CES and moderate heterogeneity (Supplementary figure 1A). Our analysis also revealed no studies missing to adjust the CES of analyses that evaluated hippocampal PV changes (Supplementary figure 1B).

The methodological quality of the selected studies was assessed using the RoB Syrcle tool, which evaluates the risk of bias concerning sequence generation, similar baseline characteristics of the groups, allocation selection, animal randomization, blinding of the researchers during the experiment and data analysis, randomization of data analysis, incomplete outcome data, selective outcome reporting, and other sources of bias. No study presented a high risk of bias for all the parameters. However, except for baseline characteristics, the risk of bias is unclear due to the absence of detailed information in the articles (Supplementary figure 2).

Discussion

Distinct animal models have been developed in the last decades based on neurochemical, genetic, and environmental perturbations associated with SCZ etiology. These models attempt to uncover neurobiological aspects of this disorder, such as new insights into cell types affected

Table 3. CES (Hedges' *g*) of PV Changes in Genetic SCZ Models Stratified into Subgroups of Studies

	PFC						HIP					
	CES	95% CLL	95% CLU	*N* analysis/ samples	I^2	*P*-value	CES	95% CLL	95% CLU	*N* analysis/ samples	I^2	*P*-value
All models	−1.10	−2.37	0.17	12/111	66.9%	0.30	−0.90	−2.48	0.68	11/186	71.7%	0.35
DISC1	−0.77	−2.18	0.64	4	74.0%		−0.42	−1.78	0.94	5	79.0%	
Dysbindin	−0.53	−2.11	1.06	4	75.1%		−1.61	−2.84	−0.38	2	83.7%	
Neuregulin/ ErBb4	−1.88	−2.22	−1.54	2	0.00%		−0.80	−1.51	−0.10	4	21.4%	
NMDAr	−0.47	−2.02	1.09	2	59.0%		NA	NA	NA	NA	NA	
All ages of PV evaluation	−0.79	−2.99	1.41	12/111	66.9%	0.37	−0.77	−3.03	1.49	10/162	73.5%	0.34
Adolescence	−0.41	−1.72	0.90	3	71.6%		−0.76	−2.21	0.70	2	58.6%	
Adulthood	−0.96	−1.84	−0.08	9	67.6%		−0.78	−1.68	0.13	8	77.3%	
All sexes	−0.38	−2.58	1.82	12/111	66.9%	0.15	−0.77	−3.03	1.49	10/162	73.5%	0.35
Male	−1.04	−1.84	−0.24	10	66.1%		−0.75	−1.68	0.13	8	77.3%	
Female	NA	NA	NA	NA	NA		−0.42	−1.78	0.94	2	58.6%	
Male and female	0.19	−0.22	0.60	2	0.00%		NA	NA	NA	1	NA	

CES = combined effect size; 95% CLL = 95% confidence interval lower limit; 95% CLU = 95% confidence interval upper limit; N = number; NA = not available.

in these models, treatment, and prevention.[33] PV interneurons have received great attention since their expression and associated functions are impaired in the PFC and HIP of patients with SCZ and individuals at high risk for psychosis.[34–36] Here, we meta-analyzed data from the most common animal models for SCZ based on pharmacological, neurodevelopmental, and genetic manipulations and confirmed a significant PV reduction in the PFC and HIP across these models, even though the effect size varies among them. We observed experimental variables in which PV abnormalities were more evident, such as the age of animal model intervention and the period of PV evaluation. In addition, comparing the PFC and HIP without differing animal models into categories, the decrease in the number of PV-positive cells and/or PV protein levels in these brain regions presented similar effect size magnitudes.

PV interneurons are the most abundant inhibitory neurons in the PFC, constituting around 40% of cortical interneurons.[37] In the HIP, they comprise 20% of inhibitory neurons, somewhat more concentrated in CA1 and CA3 than other hippocampal subregions.[38] Despite some methodological challenges in interpreting the findings,[39] decreases in the density and number of PV-positive cells have been found in prefrontal regions[3–5] and HIP[6–8] in postmortem samples from SCZ individuals. PV mRNA levels are also lower in the PFC of SCZ patients.[40,41] Despite evidence indicating that changes in cortical PV mRNA levels in SCZ are not due to fewer neurons,[41] a large transcriptomic study on bulk-postmortem tissue in SCZ showed reduced PV cell numbers instead of changes in mRNA levels.[42] Notably, a recent meta-analysis study confirmed prefrontal PV reductions at protein levels, but not in mRNA levels, in patients with SCZ.[5] Therefore, we only analyzed studies investigating PV reductions in animal models of SCZ that employed methods to evaluate protein level changes, including immunohistochemistry/ immunofluorescence and WB.

Animal Models Based on NMDA Receptor Antagonism

Animal models based on pharmacological manipulation using NMDA receptor antagonists, such as MK-801, ketamine, and PCP, have received considerable interest in preclinical studies to mimic glutamatergic dysfunction, a primary pathophysiological change seen in SCZ.[43,44] NMDA receptors control the intrinsic excitability of PV interneurons, and their antagonism reduces the firing of these interneurons, which drives pyramidal neuron disinhibition, and, consequently, greater hyperactivity of cortical and hippocampal areas.[45,46] This observation has led to the idea that functional loss of PV interneurons results from NMDA receptor hypofunction in these cells.

In humans, the administration of ketamine and PCP induces changes related to psychotic, negative, and cognitive symptoms.[47,48] Behavioral impairments associated with these symptoms are also observed after administering NMDA receptor antagonists to rodents.[49–51] Our meta-analysis revealed that NMDA receptor antagonists negatively impacted PV levels in the PFC and HIP, with MK-801 having the highest effect size in the PFC. This could be related to the greater inhibitory potency on NMDA receptors of MK-801 (IC_{50} 4.1 ± 1.6 nM) compared to ketamine and PCP (IC_{50} 508.5 ± 30.1 nM and

IC_{50} 91 ± 1.3 nM, respectively).[52] Although pharmacological animal models were primarily proposed as tools to mimic SCZ symptoms rather than uncover its pathophysiology,[21] our findings indicate that NMDA receptor antagonism could also affect PV interneurons at the molecular level.

It has been postulated that blockage of NMDA receptors on PV interneurons diminishes GABAergic inhibition, stimulating glutamatergic release, which can lead to glutamate neurotoxicity.[53] In addition, NMDA receptor-mediated neurotransmission is critical for several neurodevelopmental processes. During the neonatal period, the limbic system is highly vulnerable and sensitive to the NMDA receptor antagonism,[54,55] potentially affecting brain maturation and leading to functional and behavioral features relevant to SCZ. Also, the developmental trajectory of PV interneurons is an extended process. PV expression begins late in development (after postnatal day 7 in rodents and between 3 and 6 months in humans) and is completed around late adolescence and early adulthood.[56,57] Interestingly, this expression occurs later than other calcium-binding proteins, such as calbidin and calretinin.[58] We evaluated if the timing of NMDA receptor antagonism (neonatal, prepubertal, adolescence, or adulthood) would differently impact PV levels. Most studies in our meta-analyses exposed animals to NMDA receptor antagonists during the neonatal period and adulthood. Despite the late development of the PFC and that PV interneurons continue to mature through adolescence in both PFC and HIP,[56,59] only a few studies investigated the effects of administering NMDA receptor antagonists during this period. Our analyses indicated a significant PV reduction in the PFC independent of the age of administration, suggesting that NMDA receptor antagonism during periods in which PV interneurons have not reached their mature state did not lead to greater PV reductions. For the HIP, data from models based on NMDA receptor antagonism were inconclusive, indicating the need for further studies.

Animal Models Based on Neurodevelopmental Disruption

Early exposure, particularly during pregnancy and the perinatal period, to adverse socioenvironmental factors such as viral infections, maternal stress, maternal malnutrition, obstetric complications, and birth injuries are proposed to favor SCZ development later in life.[60] Based on these findings, animal models based on neurodevelopmental disruption to study SCZ have been employing environmental or drug manipulations during pregnancy or the perinatal periods.[61] Among these models, the MAM model has provided a translational framework considering its face, predictive, and construct validity.[62,63] At the molecular level, administration of MAM to pregnant rats at gestational day 17 leads to abnormal DNA methylation, affecting neuroblast proliferation in the offspring.[62] Several studies with the MAM model have shown molecular and functional changes associated with impairments in prefrontal and hippocampal PV interneurons.[18,31,64–66] Our meta-analysis results regarding the MAM model confirmed abnormal PV levels in HIP and were inconclusive for PFC.

Infectious diseases affecting pregnant mothers in the second to the third trimester of fetal life increased the risk of SCZ emergence in the offspring.[67] In preclinical studies, an experimental approach based on MIA models involves the administration of poly I:C, a synthetic double-stranded RNA analog that mimics viral infections, and LPS, a major component of the outer membrane of gram-negative bacteria, to pregnant rats.[67,68] We observed a significantly negative effect on prefrontal and hippocampal PV levels in the poly I:C model, whereas the LPS model negatively affects PV levels only in the HIP.

Lesioning the ventral HIP during the neonatal period has also been proposed to model neurodevelopmental disruptions related to SCZ.[69] A critical feature of this model is the narrow time window for the emergence of SCZ-like symptoms, as observed in patients.[69] In addition, lesioned rats show disruption in connections between PFC and HIP during adolescence, which is critical for brain function maturation.[70] Although our meta-analysis was inconclusive for PV changes in the PFC of lesioned rats, maturation of prefrontal interneurons in response to dopamine is disrupted in those animals, along with prefrontal glutamatergic hyperactivity.[71,72]

Other neurodevelopmental models include exposure to stressors during early life, such as maternal separation during the neonatal period and social isolation after weaning.[73–76] Insults during developmental periods can shape circuits' maturation, resulting in hyperresponsivity to stress and behavioral changes.[77,78] Indeed, children and adolescents at risk of developing SCZ may be unable to adapt to stress, and those who show greater stress sensitivity and increased anxiety tend to be the ones that develop frank SCZ later in life.[79] Stress during critical developmental periods, such as childhood and adolescence, is proposed to have a deleterious impact on PV interneurons.[80] In addition to the prolonged developmental trajectory of PV interneurons,[56–59] until early adulthood these interneurons are not entirely surrounded by the perineuronal nets (PNNs), a glycosaminoglycan matrix sheath that protect them from metabolic and oxidative damage.[81] Therefore, it is proposed that exposure to perturbations during sensitive periods, in which PV interneurons are not fully mature and protected by PNNs, may be sufficient to induce abnormalities in PV levels and behavioral and circuit deficits related to SCZ.[80] Our meta-analysis uncovered a significant negative effect on cortical PV levels of animals exposed to neonatal stress (modeled by the maternal separation procedure). In contrast, it was inconclusive in social isolation and adolescent stress models, mainly due

to the small number of studies. Only a few selected studies have analyzed PV changes in the PFC and HIP of animals exposed to stress in critical developmental periods, supporting the need for future studies to uncover the impact of stress during peripubertal and adolescent periods on PV abnormalities as a risk factor for SCZ.

Animal Models Based on Genetic Alterations

There is compelling evidence that SCZ is a highly polygenetic disorder with a complex array of risk loci.[82] Genetic mutations are an important risk factor for SCZ, in which the risk is around 9% for first-degree relatives, 13% for 1 parent affected, and 50% for both parents affected or identical twins.[83] Despite the polygenic nature of SCZ, most animal models based on genetic changes focus on deletions of single genes. Here, we restrict our analyses to the models based on the deletion of DISC1, DTNBP1, NGR1, or ErbB4, and mutations in NMDA receptor subunits.

Although cortical and hippocampal alterations in PV interneurons have been observed in DISC1 models,[84–86] our meta-analysis revealed inconclusive effects for these models in both brain areas. Another gene related to SCZ susceptibility is the *DTNBP-1*, which encodes the presynaptic protein Dysbindin-1, essential for regulating and stabilizing the dopaminergic and glutamatergic neurotransmission.[87,88] Dysbindin-1 deletions elicit alterations in NMDA receptors located in pyramidal neurons and affect presynaptic GABAergic transmission.[87] We found a significant effect in hippocampal PV levels, with no changes in the PFC. The inconclusive findings reported for the PFC may be due to the limited number of genetic studies included in this review and the different mutation types among studies.

Specific mutations in NMDA receptors or alterations in the candidate "risk" genes for the cell adhesion molecule NGR1 and its receptor ErbB4 are proposed to be involved in abnormal SCZ excitatory and inhibitory neurotransmission.[89–91] NGR1 and ErbB4 are strongly linked to the etiology of SCZ since it controls glutamatergic inputs onto PV interneurons during neurodevelopment.[92] In fact, Erbb4 deletion from inhibitory interneurons leads to analogs of in vivo neuroimaging alterations previously identified in psychosis.[93] Aligned with these findings, NGR1/ErbB4 models significantly negatively affect PV levels in both PFC and HIP. Despite not being included in our meta-analyses, PV reductions in the PFC and HIP have been reported in other models based on genetic alterations, such as the 22q11.2 deletion model.[94]

General Factors (Age of Evaluation, Species, Sex, Experimental Bias)

SCZ is often diagnosed in late adolescence and early adulthood. Along with the illness onset, patients show deficits in GABAergic transmission and impairment in cortical gamma frequency oscillations, which are thought to depend upon the normal functioning of PV interneurons.[1] We found that all animal models significantly affected PV interneurons in both brain areas when PV markers were evaluated in adulthood. Although PV interneurons continue to mature through adolescence in both PFC and HIP, leaving them more vulnerable to insults,[95] our analysis indicated that changes in PV markers evaluated at adolescence were significant only in the PFC of pharmacological SCZ models. Nevertheless, only a few selected studies evaluated hippocampal PV levels during adolescence, which may have influenced our analysis. We also found that rat models had significant PV interneuron reduction in both brain areas, whereas significant results for mice were observed only in the PFC. Regarding sex differences, most of the included studies evaluated PV changes in male rodents. Only a few studies used females or both sexes. In males, decreased PV levels were confirmed in all analyses except in the HIP of genetic models.

Overall, our meta-analyses revealed that a decrease in the number of PV-positive cells and/or PV protein levels in the PFC and HIP is consistent across distinct animal models. These findings complement evidence indicating functional impairments in PV interneurons and gain-of-function studies in which the activation of these interneurons in the PFC and HIP rescued behavioral deficits in animal models for SCZ.[96,97] These results point to PV interneuron deficits as a potential target for SCZ treatment.[98] Accordingly, preclinical studies have already shown that some antipsychotics prevent and reverse PV deficits in SCZ rodent models.[50,99] Further studies are needed to evaluate these effects in the clinics. However, it is worth mentioning that, despite these findings in animal models, PV deficits are found in postmortem brain studies in SCZ,[3,4,6,7] in which most patients underwent chronic treatment with antipsychotics.

The magnitude of PV reduction in the PFC and HIP in the animal models may be smaller than estimated in our meta-analysis. Previous data indicate that publication and other types of bias may inflate the effect sizes in animal model studies.[100,101] Although publication bias seems to be a minor problem in this review, the risk of other bias factors (selection, performance, detection, attrition, report) is unclear for most of the included studies, hampering the appraisal of the research quality. The use of guidelines like ARRIVE[102] may help to increase the quality of reports of animal studies in general, including of our field of research. Additionally, negative PV data that might not have been published could also be another poorly controlled bias source.

In sum, our findings support the significant role of PV interneurons, a specific class of GABAergic interneurons, in the pathophysiology of SCZ. Converging evidence suggests that SCZ is a disorder caused by multiple interacting factors. PV interneuron dysfunction is a hallmark in its etiology and is well established in clinical

and basic science studies. This meta-analysis confirmed PV reductions in the PFC and HIP of widely used animal models in SCZ research, even though further studies are needed to explore these abnormalities in specific subgroups (for instance, in female animals and across different developmental periods).

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Funding

T.S.S acknowledges a Ph.D. fellowship from the Coordination for the Improvement of Higher Education Personnel-Brazil (CAPES, #88887.334572/2019-00). D.d.S.F acknowledges a Ph.D. fellowship from the São Paulo Research Foundation (FAPESP, 19/24591-4). C.L.d.O. is sponsored by Alexander von Humboldt Foundation. F.S.G. and F.V.G. receive grants from FAPESP (17/24304-0 to F.S.G., and 18/17597-3 to F.V.G.).

Author Contributions

T.S.-S.: methodology, data curation, formal analysis, writing—original draft, review and editing. D.d.S.F.: methodology, data curation, formal analysis, writing—review and editing. C.L.d.O.: conceptualization, methodology, writing—review and editing. F.S.G.: conceptualization, methodology, writing—review and editing. F.V.G.: conceptualization, methodology, writing—review and editing.

References

1. Gonzalez-Burgos G, Cho RY, Lewis DA. Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biol Psychiatry.* 2015;77(12):1031–1040. doi:10.1016/j.biopsych.2015.03.010.
2. Nahar L, Delacroix BM, Nam HW. The role of parvalbumin interneurons in neurotransmitter balance and neurological disease. *Front Psychiatry.* 2021;12:1–14. doi:10.3389/fpsyt.2021.679960.
3. Beasley CL, Reynolds GP. Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. *Schizophr Res.* 1997;24(3):349–355. doi:10.1016/S0920-9964(96)00122-3.
4. Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. *Biol Psychiatry.* 2002;52(7):708–715. doi:10.1016/S0006-3223(02)01360-4.
5. Kaar SJ, Angelescu I, Marques TR, Howes OD. Prefrontal parvalbumin interneurons in schizophrenia: a meta-analysis of post-mortem studies. *J Neural Transm.* 2019;126(12):1637–1651. doi:10.1007/s00702-019-02080-2.
6. Zhang ZJ, Reynolds GP. A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. *Schizophr Res.* 2002;55(1–2):1–10. doi:10.1016/S0920-9964(01)00188-8.
7. Konradi C, Yang CK, Zimmerman EI, *et al*. Hippocampal interneurons are abnormal in schizophrenia. *Schizophr Res.* 2011;131(1–3):165–173. doi:10.1016/J.SCHRES.2011.06.007.
8. Farmer CB, Roach EL, Bice LR, *et al*. Excitatory and inhibitory imbalances in the trisynaptic pathway in the hippocampus in schizophrenia: a postmortem ultrastructural study. *J Neural Transm.* 2013;130(7):949–965. doi:10.1007/s00702-023-02650-5.
9. Steullet P, Cabungcal JH, Coyle J, *et al*. Oxidative stress-driven parvalbumin interneuron impairment as a common mechanism in models of schizophrenia. *Mol Psychiatry.* 2017;22(7):936–943. doi:10.1038/mp.2017.47.
10. Kim H, Ährlund-Richter S, Wang X, Deisseroth K, Carlén M. Prefrontal parvalbumin neurons in control of attention. *Cell.* 2016;164(1–2):208–218. doi:10.1016/j.cell.2015.11.038.
11. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature.* 2009;459(7247):698–702. doi:10.1038/nature07991.
12. Wulff P, Ponomarenko AA, Bartos M, *et al*. Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons. *Proc Natl Acad Sci U S A.* 2009;106(9):3561–3566. doi:10.1073/pnas.0813176106.
13. Amilhon B, Huh CYL, Manseau F, *et al*. Parvalbumin interneurons of hippocampus tune population activity at theta frequency. *Neuron.* 2015;86(5):1277–1289. doi:10.1016/j.neuron.2015.05.027.
14. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci.* 2016;17(8):524–532. doi:10.1016/j.physbeh.2017.03.040.
15. Knight S, McCutcheon R, Dwir D, *et al*. Hippocampal circuit dysfunction in psychosis. *Transl Psychiatry.* 2022;12(1):1–13. doi:10.1038/s41398-022-02115-5.
16. Grace AA, Gomes FV. The circuitry of dopamine system regulation and its disruption in schizophrenia: insights into treatment and prevention. *Schizophr Bull.* 2019;45(1):148–157. doi:10.1093/schbul/sbx199.
17. Sonnenschein SF, Gomes FV, Grace AA. Dysregulation of midbrain dopamine system and the pathophysiology of schizophrenia. *Front Psychiatry.* 2020;11:1–11. doi:10.3389/fpsyt.2020.00613.
18. Lodge DJ, Grace AA. Aberrant hippocampal regulation of dopamine neuron responsivity in an animal model of schizophrenia. *Schizophr Bull.* 2007;33(2):407.
19. Bialon M, Wasik A. Advantages and limitations of animal schizophrenia models and limitations of animal schizophrenia models. *Int J Mol Sci.* 2022;1:32.
20. Eyles DW. How do established developmental risk-factors for schizophrenia change the way the brain develops? *Transl Psychiatry.* 2021;11(1):158. doi:10.1038/s41398-021-01273-2.
21. Uliana DL, Gomes FV, Grace AA. Update on current animal models for schizophrenia: are they still useful?

Curr Opin Psychiatry. 2023;36(3):172–178. doi:10.1097/YCO.0000000000000854.

22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.
23. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2006;5:210. doi:10.1186/s13643-016-0384-4.
24. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol.* 2014;14:43. doi:10.1186/1471-2288-14-43.
25. Sawilowsky SS. New effect size rules of thumb. *J Mod Appl Stat Methods*. 2009;8(2):597–599. doi:10.22237/jmasm/1257035100.
26. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biol Rev Camb Philos Soc.* 2007;82(4):591–605. doi:10.1111/j.1469-185X.2007.00027.x.
27. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560. doi:10.1136/bmj.327.7414.557.
28. Sabbagh JJ, Murtishaw AS, Bolton MM, Heaney CF, Langhardt M, Kinney JW. Chronic ketamine produces altered distribution of parvalbumin-positive cells in the hippocampus of adult rats. *Neurosci Lett.* 2013;550:69–74. doi:10.1016/j.neulet.2013.06.040.
29. Shepard R, Heslin K, Hagerdorn P, Coutellier L. Downregulation of Npas4 in parvalbumin interneurons and cognitive deficits after neonatal NMDA receptor blockade: relevance for schizophrenia. *Transl Psychiatry.* 2019;9(1):99. doi:10.1038/s41398-019-0436-3.
30. Boksa P, Zhang Y, Nouel D, Wong A, Wong TP. Early development of parvalbumin-, somatostatin-, and cholecystokinin-expressing neurons in rat brain following prenatal immune activation and maternal iron deficiency. *Dev Neurosci.* 2017;38(5):342–353. doi:10.1159/000454677.
31. Maćkowiak M, Latusz J, Głowacka U, Bator E, Bilecki W. Adolescent social isolation affects parvalbumin expression in the medial prefrontal cortex in the MAM-E17 model of schizophrenia. *Metab Brain Dis.* 2019;34(1):341–352. doi:10.1007/s11011-018-0359-3.
32. Lee FHF, Zai CC, Cordes SP, Roder JC, Wong AHC. Abnormal interneuron development in disrupted-in-schizophrenia-1 L100P mutant mice. *Mol Brain*. 2013;6:20.
33. Uliana DL, Zhu X, Gomes FV, Grace AA. Using animal models for the studies of schizophrenia and depression: the value of translational models for treatment and prevention. *Front Behav Neurosci.* 2022;16:1–15. doi:10.3389/fnbeh.2022.935320.
34. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* 2012;35(1):57–67. doi:10.1016/j.tins.2011.10.004.
35. Merritt K, McCutcheon RA, Aleman A, *et al*. Variability and magnitude of brain glutamate levels in schizophrenia: a meta and mega-analysis. *Mol Psychiatry.* 2023. doi:10.1038/s41380-023-01991-7.
36. Modinos G, Şimşek F, Azis M, *et al*. Prefrontal GABA levels, hippocampal resting perfusion and the risk of psychosis. *Neuropsychopharmacology.* 2018;43(13):2652–2659. doi:10.1038/s41386-017-0004-6.
37. Llorca A, Deogracias R. Origin, development, and synaptogenesis of cortical interneurons. *Front Neurosci.* 2022;16:929469. doi:10.3389/fnins.2022.929469.
38. Pelkey KA, Chittajallu R, Craig MT, Tricoire L, Wester JC, McBain CJ. Hippocampal gabaergic inhibitory interneurons. *Physiol Rev.* 2017;97(4):1619–1747. doi:10.1152/physrev.00007.2017.
39. Dienel SJ, Fish KN, Lewis DA. The nature of prefrontal cortical GABA neuron alterations in schizophrenia: markedly lower somatostatin and parvalbumin gene expression without missing neurons. *Am J Psychiatry.* 2023;180(7):495–507. doi:10.1176/APPI.AJP.20220676.
40. Volk DW, Sampson AR, Zhang Y, Edelson JR, Lewis DA. Cortical GABA markers identify a molecular subtype of psychotic and bipolar disorders. *Psychol Med.* 2016;46(12):2501–2512. doi:10.1017/S0033291716001446.
41. Enwright JF, Huo Z, Arion D, *et al*. Transcriptome alterations of prefrontal cortical parvalbumin neurons in schizophrenia. *Mol Psychiatry.* 2018;23(7):1606–1613. doi:10.1038/MP.2017.216.
42. Toker L, Mancarci BO, Tripathy S, Pavlidis P. Transcriptomic evidence for alterations in astrocytes and parvalbumin interneurons in subjects with bipolar disorder and schizophrenia. *Biol Psychiatry.* 2018;84(11):787–796. doi:10.1016/J.BIOPSYCH.2018.07.010.
43. Gonzalez-Burgos G, Lewis DA. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. *Schizophr Bull.* 2012;38(5):950–957. doi:10.1093/schbul/sbs010.
44. Howes O, Mccutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol.* 2015;29(2):97–115. doi:10.1177/0269881114563634.
45. Korotkova T, Fuchs EC, Ponomarenko A, von Engelhardt J, Monyer H. NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representations, and working memory. *Neuron.* 2010;68(3):557–569. doi:10.1016/j.neuron.2010.09.017.
46. Wang HX, Gao WJ. Cell type-specific development of NMDA receptors in the interneurons of rat prefrontal cortex. *Neuropsychopharmacology.* 2009;34:2028–2040. doi:10.1038/npp.2009.20.
47. Luby E, Cohen B, Rosenbaum G, *et al*. Study schizophrenomimetic drug sernyl. *AMA Arch Neurol Psychiatry*. 1959;113:119. doi:10.1001/archneurpsyc.1959.02340150095011.
48. Krysta JH, Karper LP, Seibyl JP, *et al*. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry.* 1994;51(3):199–214. doi:10.1001/archpsyc.1994.03950030035004.
49. Abekawa T, Ito K, Nakagawa S, Koyama T. Prenatal exposure to an NMDA receptor antagonist, MK-801 reduces density of parvalbumin-immunoreactive GABAergic neurons in the medial prefrontal cortex and enhances phencyclidine-induced hyperlocomotion but not behavioral sensitization to methamphetamine. *Psychopharmacology.* 2007;192(3):303–316. doi:10.1007/s00213-007-0729-8.
50. Gomes FV, Issy AC, Ferreira FR, *et al*. Cannabidiol attenuates sensorimotor gating disruption and molecular changes induced by chronic antagonism of NMDA receptors in mice. *Intl J Neuropsychopharmacol*. 2015;18(5):1–10. doi:10.1093/ijnp/pyu041.

51. Jenkins TA, Harte MK, McKibben CE, *et al*. Disturbances in social interaction occur along with pathophysiological deficits following sub-chronic phencyclidine administration in the rat. *Behav Brain Res*. 2008;194(2):230–235. doi:10.1016/j.bbr.2008.07.020.
52. Wallach J, Kang H, Colestock T, *et al*. Pharmacological investigations of the dissociative "Legal Highs" diphenidine, methoxphenidine and analogues. *PLoS One*. 2016;11(6):e0157021. doi:10.1371/journal.pone.0157021.
53. Olney JW, Newcomer JW, Farber NB. NMDA receptor hypofunction model of schizophrenia. *J Psychiatr Res*. 1999;33(6):523–533. doi:10.1016/S0022-3956(99)00029-1.
54. Toriumi K, Mouri A, Narusawa S, *et al*. Prenatal NMDA receptor antagonism impaired proliferation of neuronal progenitor, leading to fewer glutamatergic neurons in the prefrontal cortex. *Neuropsychopharmacology*. 2012;37(6):1387–1396. doi:10.1038/npp.2011.324.
55. Farber NB, Kim SH, Dikranian K, Jiang XP, Heinkel C. Receptor mechanisms and circuitry underlying NMDA antagonist neurotoxicity. *Mol Psychiatry*. 2002;7(1):32–43. doi:10.1038/sj/mp/4000912.
56. Caballero A, Tseng KY. GABAergic function as a limiting factor for prefrontal maturation during adolescence. *Trends Neurosci*. 2016;39(7):441–448. doi:10.1016/j.tins.2016.04.010.
57. Grateron L, Cebada-Sanchez S, Marcos P, *et al*. Postnatal development of calcium-binding proteins immunoreactivity (parvalbumin, calbindin, calretinin) in the human entorhinal cortex. *J Chem Neuroanat*. 2003;26(4):311–316. doi:10.1016/J.JCHEMNEU.2003.09.005.
58. Caballero A, Diah KC, Tseng KY. Region-specific upregulation of parvalbumin-, but not calretinin-positive cells in the ventral hippocampus during adolescence. *Hippocampus*. 2013;23(12):1331–1336. doi:10.1002/HIPO.22172.
59. Caballero A, Flores-Barrera E, Cass DK, Tseng KY. Differential regulation of parvalbumin and calretinin interneurons in the prefrontal cortex during adolescence. *Brain Struct Funct*. 2014;219(1):395–406. doi:10.1007/s00429-013-0508-8.
60. Cattane N, Richetto J, Cattaneo A. Prenatal exposure to environmental insults and enhanced risk of developing Schizophrenia and Autism Spectrum Disorder: focus on biological pathways and epigenetic mechanisms. *Neurosci Biobehav Rev*. 2020;117:253–278. doi:10.1016/j.neubiorev.2018.07.001.
61. Tendilla-Beltrán H, Sanchez-Islas NC, Marina-Ramos M, *et al*. The prefrontal cortex as a target for atypical antipsychotics in schizophrenia, lessons of neurodevelopmental animal models. *Prog Neurobiol*. 2021;199:101967. doi:10.1016/j.pneurobio.2020.101967.
62. Moore H, Jentsch JD, Ghajarnia M, Geyer MA, Grace AA. A neurobehavioral systems analysis of adult rats exposed to methylazoxymethanol acetate on E17: implications for the neuropathology of schizophrenia. *Biol Psychiatry*. 2006;60(3):253–264. doi:10.1016/j.biopsych.2006.01.003.
63. Gomes FV, Rincón-Cortés M, Grace AA. Adolescence as a period of vulnerability and intervention in schizophrenia: insights from the MAM model. *Neurosci Biobehav Rev*. 2016;70:260–270. doi:10.1016/j.neubiorev.2016.05.030.
64. Gill KM, Grace AA. Corresponding decrease in neuronal markers signals progressive parvalbumin neuron loss in MAM schizophrenia model. *Int J Neuropsychopharmacol*. 2014;17(3):1609–1619. doi:10.1017/S146114571400056X.
65. Gastambide F, Cotel MC, Gilmour G, O'Neill MJ, Robbins TW, Tricklebank MD. Selective remediation of reversal learning deficits in the neurodevelopmental MAM model of schizophrenia by a novel mGlu5 positive allosteric modulator. *Neuropsychopharmacology*. 2012;37(4):1057–1066. doi:10.1038/npp.2011.298.
66. Penschuck S, Flagstad P, Didriksen M, Leist M, Michael-Titus AT. Decrease in parvalbumin-expressing neurons in the hippocampus and increased phencyclidine-induced locomotor activity in the rat methylazoxymethanol (MAM) model of schizophrenia. *Eur J Neurosci*. 2006;23(1):279–284. doi:10.1111/j.1460-9568.2005.04536.x.
67. Haddad FL, Patel SV, Schmid S. Maternal immune activation by Poly I:C as a preclinical model for neurodevelopmental disorders: a focus on autism and schizophrenia. *Neurosci Biobehav Rev*. 2020;113:546–567. doi:10.1016/j.neubiorev.2020.04.012.
68. Wischhof L, Irrsack E, Osorio C, Koch M. Prenatal LPS-exposure - a neurodevelopmental rat model of schizophrenia - differentially affects cognitive functions, myelination and parvalbumin expression in male and female offspring. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015;57:17–30. doi:10.1016/j.pnpbp.2014.10.004.
69. Lipska BK, Jaskiw GE, Weinberger DR. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. *Neuropsychopharmacology*. 1993;9(1):67–75. doi:10.1038/npp.1993.44.
70. Tseng KY, Lewis BL, Lipska BK, O'Donnell P. Post-pubertal disruption of medial prefrontal cortical dopamine–glutamate interactions in a developmental animal model of schizophrenia. *Biol Psychiatry*. 2007;62(7):730–738. doi:10.1016/j.biopsych.2006.10.012.
71. O'Donnell P, Lewis BL, Weinberger DR, Lipska BK. Neonatal hippocampal damage alters electrophysiological properties of prefrontal cortical neurons in adult rats. *Cereb Cortex*. 2002;12(9):975–982. doi:10.1093/cercor/12.9.975.
72. Tseng KY, Lewis BL, Hashimoto T, *et al*. Neurobiology of disease a neonatal ventral hippocampal lesion causes functional deficits in adult prefrontal cortical interneurons. *J Neurosci*. 2008;28(48):12691–12699. doi:10.1523/JNEUROSCI.4166-08.2008.
73. do Prado CH, Narahari T, Holland FH, Lee H-N, Murthy SK, Brenhouse HC. Effects of early adolescent environmental enrichment on cognitive dysfunction, prefrontal cortex development, and inflammatory cytokines after early life stress. *Dev Psychobiol*. 2016;58(4):482–491. doi:10.1002/dev.21390.
74. Holland FH, Ganguly P, Potter DN, Chartoff EH, Brenhouse HC. Early life stress disrupts social behavior and prefrontal cortex parvalbumin interneurons at an earlier time-point in females than in males. *Neurosci Lett*. 2014;566:131–136. doi:10.1016/j.neulet.2014.02.023.
75. Ueno H, Suemitsu S, Murakami S, *et al*. Region-specific impairments in parvalbumin interneurons in social isolation-reared mice. *Neuroscience*. 2017;359:196–208. doi:10.1016/j.neuroscience.2017.07.016.
76. Harte MK, Powell SB, Swerdlow NR, Geyer MA, Reynolds GP. Deficits in parvalbumin and calbindin immunoreactive cells in the hippocampus of isolation reared rats. *J Neural Transm*. 2007;114(7):893–898. doi:10.1007/s00702-007-0627-6.
77. Ganguly P, Holland FH, Brenhouse HC. Functional uncoupling NMDAR NR2A subunit from PSD-95 in the prefrontal cortex: effects on behavioral dysfunction and parvalbumin loss after early-life stress. *Neuropsychopharmacology*. 2015;40(12):2666–2675. doi:10.1038/npp.2015.134.

78. Page CE, Coutellier L. Adolescent stress disrupts the maturation of anxiety-related behaviors and alters the developmental trajectory of the prefrontal cortex in a sex- and age-specific manner. *Neuroscience.* 2018;390:265–277. doi:10.1016/j.neuroscience.2018.08.030.
79. Pruessner M, Iyer SN, Faridi K, Joober R, Malla AK. Stress and protective factors in individuals at ultra-high risk for psychosis, first episode psychosis and healthy controls. *Schizophr Res.* 2011;129(1):29–35. doi:10.1016/j.schres.2011.03.022.
80. Gomes FV, Zhu X, Grace AA. Stress during critical periods of development and risk for schizophrenia. *Schizophr Res.* 2019;213:107–113. doi:10.1016/j.schres.2019.01.030.
81. Cabungcal JH, Steullet P, Morishita H, *et al*. Perineuronal nets protect fast-spiking interneurons against oxidative stress. *Proc Natl Acad Sci U S A.* 2013;110(22):9130–9135. doi:10.1073/pnas.1300454110.
82. Trubetskoy V, Pardiñas AF, Qi T, *et al.*; Indonesia Schizophrenia Consortium. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature.* 2022;604(7906):502–508. doi:10.1038/s41586-022-04434-5.
83. Janoutová J, Janáčková P, Šerý O, *et al*. Epidemiology and risk factors of schizophrenia. *Neuro Endocrinol Lett.* 2016;37(1):1–8.
84. Shen S, Lang B, Nakamoto C, *et al*. Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated Disc1. *J Neurosci.* 2008;28(43):10893–10904. doi:10.1523/JNEUROSCI.3299-08.2008.
85. Hikida T, Jaaro-Peled H, Seshadri S, *et al*. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. *Proc Natl Acad Sci U S A.* 2007;104(36):14501–14506. doi:10.1073/pnas.0704774104.
86. Deng D, Jian C, Lei L, *et al*. A prenatal interruption of DISC1 function in the brain exhibits a lasting impact on adult behaviors, brain metabolism, and interneuron development. *Oncotarget*. 2017;8(49):84798–84817. doi:10.18632/oncotarget.21381.
87. Trantham-Davidson H, Lavin A. Loss of dysbindin-1 affects GABAergic transmission in the PFC. *Psychopharmacology.* 2019;236(11):3291–3300. doi:10.1007/s00213-019-05285-1.
88. Carlson GC, Talbot K, Halene TB, *et al*. Dysbindin-1 mutant mice implicate reduced fast-phasic inhibition as a final common disease mechanism in schizophrenia. *Proc Natl Acad Sci U S A.* 2011;108(43):E962–E970. doi:10.1073/pnas.1109625108.
89. Yang JM, Zhang J, Chen XJ, *et al*. Development of GABA circuitry of fast-spiking basket interneurons in the medial prefrontal cortex of erbb4-mutant mice. *J Neurosci.* 2013;33(50):19724–19733. doi:10.1523/JNEUROSCI.1584-13.2013.
90. delPino I, García-Frigola C, Dehorter N, *et al*. Erbb4 deletion from fast-spiking interneurons causes schizophrenia-like phenotypes. *Neuron.* 2013;79(6):1152–1168. doi:10.1016/j.neuron.2013.07.010.
91. Gandal MJ, Sisti J, Klook K, *et al*. GABA B-mediated rescue of altered excitatory-inhibitory balance, gamma synchrony and behavioral deficits following constitutive NMDAR-hypofunction. *Transl Psychiatry.* 2012;2(7):e142. doi:10.1038/tp.2012.69.
92. Wen L, Lu Y, Zhu XH, *et al*. Neuregulin 1 regulates pyramidal neuron activity via ErbB4 in parvalbumin-positive interneurons. *Proc Natl Acad Sci U S A.* 2010;107(3):1211–1216. doi:10.1073/pnas.0910302107.
93. Kiemes A, Serrano Navacerrada ME, Kim E, *et al*. Erbb4 deletion from inhibitory interneurons causes psychosis-relevant neuroimaging phenotypes. *Schizophr Bull.* 2022;1:12. doi:10.1093/schbul/sbac192.
94. Al-Absi AR, Qvist P, Okujeni S, *et al*. Layers II/III of prefrontal cortex in Df(h22q11)/+ mouse model of the 22q11.2 deletion display loss of parvalbumin interneurons and modulation of neuronal morphology and excitability. *Mol Neurobiol.* 2020;57(12):4978–4988. doi:10.1007/s12035-020-02067-1.
95. Ruden JB, Dugan LL, Konradi C. Parvalbumin interneuron vulnerability and brain disorders. *Neuropsychopharmacology.* 2021;46(2):279–287. doi:10.1038/s41386-020-0778-9.
96. Shin Yim Y, Park A, Berrios J, *et al*. Reversing behavioural abnormalities in mice exposed to maternal inflammation. *Nature.* 2017;549(7673):482–487. doi:10.1038/nature23909.
97. Canetta S, Bolkan S, Padilla-Coreano N, *et al*. Maternal immune activation leads to selective functional deficits in offspring parvalbumin interneurons. *Mol Psychiatry.* 2016;21(7):956–968. doi:10.1038/mp.2015.222.
98. Gomes FV, Grace AA. Beyond dopamine receptor antagonism: new targets for schizophrenia treatment and prevention. *Int J Mol Sci.* 2021;22(9):4467. doi:10.3390/IJMS22094467.
99. Braun I, Genius J, Grunze H, Bender A, Möller H-J, Rujescu D. Alterations of hippocampal and prefrontal GABAergic interneurons in an animal model of psychosis induced by NMDA receptor antagonism. *Schizophr Res.* 2007;97(1–3):254–263. doi:10.1016/j.schres.2007.05.005.
100. Sena ES, van der Worp HB, Bath PM, Howells DW, Macleod MR. Publication bias in reports of animal stroke studies leads to major overstatement of efficacy. *PLoS Biol.* 2010;8(3):e1000344. doi:10.1371/journal.pbio.1000344.
101. Crossley NA, Sena ES, Goehler J, *et al*. Empirical evidence of bias in the design of experimental stroke studies: a metaepidemiologic approach. *Stroke.* 2008;39(3):929–934. doi:10.1161/STROKEAHA.107.498725.
102. Percie du Sert N, Hurst V, Ahluwalia A, *et al*. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. *PLoS Biol.* 2020;18(7):e3000410. doi:10.1371/journal.pbio.3000410.