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Abnormalities in behavior relevant to schizophrenia in social isolation rearing rodent models: A systematic review and meta-analysis

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Abstract

Background: Social isolation (SI) induces alterations in brain development, leading to behavioral impairments similar to schizophrenia-like phenotypes. A developmental model of schizophrenia is achieved by SI of weanling rats and mice. This study conducts a systematic review and meta-analysis to evaluate the behavioral consequences of SI on rodents comprehensively and explore potential heterogeneous factors reflective of schizophrenia-related phenotypes.

Methods: Employing a meticulous search strategy across PubMed, Web of Science, Embase, Wan fang and CNKI, this study adheres to PRISMA guidelines. The analysis includes studies examining the impact of post-weaning social isolation rearing effects on behavioral outcomes, such as Elevated Plus Maze (EPM) performance, Open Field Test (OFT), Pre-pulse Inhibition (PPI) and Morris Water Maze (MWM). The study protocol is registered with PROSPERO, number CRD420250610010.

Results: A total of 43 articles were included. SI rodents in the EPM group exhibit a Mean Difference (MD) of -0.29 (95% CI: (-0.58, -0.00)) in adulthood. SI rodents show a significant overall effect on anxiety-like behavior, reduced open-arm exploration. Notable inter-study heterogeneity was observed. SI significantly increased locomotor activity in OFT. Adulthood results show a MD of 1.53 (95% CI: (1.12, 1.93)). However, studies showed substantial heterogeneity. In mice, a MD showing average reductions of -0.59 (95% CI: (−1.18, -0.00)) for PPI (66-70 low), -0.16 (95% CI: (−0.63, 0.31)) for PPI (71-76 medium) and -0.86 (95% CI = (−1.32, −0.40)) for PPI (77- high) with SI when compared with healthy controls. The heterogeneity across studies was low. In rats, all pre-pulse intensities showed significant PPI reductions in SI groups ($p < 0.0001$ for all), though substantial heterogeneity was observed, possibly linked to strain differences (e.g., Wistar vs. Sprague-Dawley) and variations in isolation onset age. The overall effect of SI on MWM performance was statistically significant, shows a mean difference of 0.97 (95% CI: (0.31, 1.62)), indicating altered spatial learning/memory. However, extreme inter-study heterogeneity was present. The overall data suggested that SI had a large effect on exacerbating schizophrenia-like behaviors, but high heterogeneity was found in several behavioral analyses.

Conclusion: This systematic review and meta-analysis offer a comprehensive overview of behavioral consequences linked to post-weaning social isolation rearing in rodents. The data suggested that SI had a significant overall effect on exacerbating schizophrenia-like behaviors in animal models. More high-quality studies with longer follow-up times are needed to strengthen this evidence. It has promoted the understanding of the impact of SI on neurodevelopment and put forward suggestions for future research in related fields.

Introduction

The prevalence of schizophrenia is about 1% worldwide, and patients often suffer from disturbances in perception, thinking, emotion, and behavior and incoordination of mental activities [1]. The psychosocial hypothesis is a widely recognized etiology of schizophrenia, which suggests that the onset of schizophrenia occurs at a critical time during early development. It is believed that environmental stresses at critical times in early development alter brain development leading to behavioral deficits in adulthood. The social isolation (SI) model is a representative paradigm of the psychosocial hypothesis, in which mice are isolated immediately after weaning (P21) to perturb neurodevelopmental trajectories, leading to persistent behavioral deficits in adulthood. Therefore, an in-depth study of the SI model is of great significance for understanding the etiology of schizophrenia, screening of therapeutic drugs, and intervention measures [2].

While modeling the positive symptoms of schizophrenia (hallucinations and delusions) in animals is inherently difficult, SI rearing effectively models core negative and cognitive symptoms, including impairments in cognition, memory, emotion, and social interaction. Specifically, SI rearing in rodents consistently induces a range of alterations such as increased anxiety- and depression-like behaviors, deficits in sensorimotor gating, and impaired learning and memory [3]. This meta-analysis will quantitatively synthesize the effects of post-weaning social isolation rearing in rodents on key schizophrenia-relevant behavioral domains. We selected four well-established behavioral tests: the Elevated Plus Maze (EPM) and Open Field Test (OFT) to assess anxiety and exploratory behavior/ activity, Pre-pulse Inhibition (PPI) to measure sensorimotor gating, and the Morris Water Maze (MWM) to evaluate spatial learning and memory.

Materials and methods

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Key words: *schizophrenia, rodent models, social isolation, behavioral analysis*

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Search strategy

Five online databases (PubMed, Web of Science, Embase, Wanfang, CNKI) were systematically searched until May 30, 2025 to identify experimental studies investigating schizophrenia-like behaviors induced by SI in rodent models. The search strategy focused on three key domains: social isolation (intervention), schizophrenia-like behavior (outcome), and rats/mice (population). We using the following search:

((("Social Isolation"[Mesh]) OR ((((Isolation, Social[Title/Abstract]) OR (Social Exclusion[Title/Abstract])) OR (Exclusion, Social[Title/Abstract])) OR (Social Exclusions[Title/Abstract])))) AND (("Schizophrenia"[Mesh]) OR (((((Schizophrenias[Title/Abstract]) OR (Schizophrenic Disorders[Title/Abstract])) OR (Disorder, Schizophrenic[Title/Abstract])) OR (Schizophrenic Disorder[Title/Abstract])) OR (SCZ[Title/Abstract])))) AND (("Behavior"[Mesh]) OR (behaviors[Title/Abstract]))

After excluding duplicate references, we screened titles and abstracts to identify potentially relevant articles that fit the inclusion criteria. The titles and abstracts of the studies obtained through the search were examined by two reviewers in order to determine article inclusion. The next step is to conduct a full-text analysis of the remaining articles.

Data extraction

Experimental studies that assessed the effects of schizophrenia-like behavior in rodents were considered eligible. The following inclusion criteria were used:

Article type: Experimental studies.

Participants: Rodents. Genetically modified mouse were also excluded.

Intervention: social isolation rearing as an intervention.

Comparison: Except for social isolation rearing, the rest of the interventions (room, handlers, diet, light cycle, and enrichment provision) were the same in the experimental group and the control group.

Outcomes: Results from at least one of the experiments involving EPM, OFT, PPI or MWM.

There was no language, publication date or other restrictions.

In the first selection phase (title and abstract), exclusion criteria were applied in the following order: (1) reviews/ theoretical articles (2) wrong population (not rodents) and (3) wrong intervention (add Surgical and pharmacological methods). In the second selection phase (full texts), exclusion criteria were applied in the following order: (1) full text not available (2) no control group or condition (3) no OFT, EPM, PPI or MWM experiments (4) no uniform experimental data (5) no appropriate behavioral assessment.

Data was extracted from each article by Wanqi Jin and Minyue Zhang. To resolve discrepancies, a third reviewer Yumu Guo was consulted. Comprehensive information was extracted from each article, encompassing details such as authors, title, sample size, species, strain, and age of the subjects, types of outcomes tested, as well as control animals. For every comparison, the numerical variable used to evaluate the behavior of animals was meticulously extracted in the form of mean ± standard deviation (SD). When these data were available only in graphical form, the program WebPlotDigitizer [4] was utilized to convert graphically represented data into numerical values using the distance measurement function [5]. A detailed information with all variables is available in Tables 1-4. For studies disclosing standard error of the mean, the SD was calculated by dividing it by the square root of the sample size.

Statistical analysis

All statistical analyses were performed using Cochrane Review Manager 5.3. A random-effects model was selected as the primary meta-analytic approach due to anticipated heterogeneity across studies. Meta-analyses were conducted only when ≥ 3 studies reported comparable outcome data. All primary results on the four outcomes of interest, OFT, EPM, PPI and MWM are presented for the overall sample (stratified by species). Hedge's g was used as the pooled measurement of effect size as it is preferred over Cohen's d for small samples (which are common in animal studies). Cochran's Q test and the I^2 index were used to test heterogeneity between studies. Data were presented in Forest plots as effect size ± 95% confidence interval (CI). Results were considered significant when CIs did not contain zero, associated with $p < 0.05$.

Results

Search results 1745 articles were identified for consideration in the present meta-analysis. 41 studies were eligible for inclusion in this meta-analysis (Tables 1-4). Of the 41 included studies: 10 assessed anxiety-like behavior using EPM, 6 evaluated locomotor activity *via* OFT, 31 measured sensorimotor gating with PPI, 5 examined spatial cognition through the MWM. Each article underwent a detailed data extraction process (Figure 1), as described in the methodology section.

Outcome

EPM: In the EPM trial, the association between social isolation rodents and anxiety in schizophrenia-like behaviors was described in studies using EPMs to examine this issue (Figure 2). A total of 9 articles met the inclusion criteria and were included in EPM [6-14].

The overall effect of social isolation rearing on EPM was significant (95% confidence interval =-0.29 (-0.58,-0.00), Z=1.98, p=0.05), and inter-study heterogeneity was significant (I^2=79%, Chi^2=37.95, df=8). Suggesting that the association between social isolation and increased EPM performance was statistically significant, although this reduced schizophrenia-like behaviors was only significant in mice (95% confidence interval=-0.41 (-0.78, -0.03) of mice) (Figure 2).

OFT: Six studies [15-20] quantified the effects of SI on exploratory behavior using the OFT (Figure 3). SI induced significant hyperlocomotion (MD=1.53, 95% Cl (1.12, 1.93); Z=7.43, $p < 0.00001$) with substantial between-study heterogeneity (I^2=91%, χ^2=57.01, df=5, $p < 0.00001$).

PPI: In the PPI trial, 31articles were included that described the use of PPI to examine the effects of social isolation rearing on cognitive and sensory impairments in schizophrenic behavior (Figures 4 and 5) [13,15,16,19,21-43].

In the mice group, it (Figure 4) shows the forest plot for PPI(66-70 low), PPI(71-76 medium) and PPI(77- high) SDs with 95% confidence intervals and a summary mean difference showing average reductions of PPI(66-70 low) (95% CI=-0.59(−1.18, -0.00), p=0.05) , PPI(71-76 medium) (95% CI=-0.16(−0.63, 0.31), p=0.51) and PPI(77- high) (95% CI=-0.86(−1.32, −0.40), p=0.0003) in mice with SI when compared with healthy controls. The heterogeneity across studies was low for both PPI (66-70 low) (I^2=0%, Chi^2=0.06), PPI (71-76 medium) (I^2=38%, Chi^2=3.20) and PPI (77- high)) (I^2=90%, Chi^2=39.67).

Table 1. Studies on EPM

Reference/Year	Species	Sex	Format of separation	Age of testing	Test	Injection	Data	Variance Measure	SI			GH		
									SI	vm	n	mean	vm	n
Hiroyuki Koikea,b 2009	Mouse-ICR	M	P21-P49	P49	EPM	yes	time(s)	SEM	9.90	20.28	19	16.25	31.06	17
Departamento 2002	Mouse-albino Alderly Park strain	M	8-10weeks		EPM	yes	time(s)	SEM	7.93	18.44	11	6.28	23.28	12
Qian Huang1 2017	Mouse- C57BL/6	M,F	P21-65	P65,66,68	EPM	yes	time(s)	SEM	6.28	23.28	12	7.93	18.44	11
Susanna 2008	Mouse- C57BL/6	M,F	P22-49	P50	EPM	no	%Percentage open arm time	SEM	0.04	44.94	11	0.05	77.92	15
Valentine Bouet 2011	Mouse-NMRI	M	P21	P120	EPM	yes	%Percentage open arm time	SEM	33.00	8.00	16	44.00	8.00	16
Lan Sun 2018	Rat-Sprague-Dawley	M	P21-56	P57	EPM	no	time(s)	SEM	37.36	16.30	9	44.07	19.16	9
MIGUEL 2001	Rat-Wistar	M,F	P20-P 40,70,90	P70	EPM	no	time(s)	SEM	21.29	50.10	15	23.48	96.34	15
Sarah M 2010	Rat-Sprague-Dawley	M	P21-70	P70-73	EPM	yes	%Percentage open arm time	SEM	16.38	23.00	8	18.20	17.23	8
N. R. SCIOLINO 2010	Rat-Sprague-Dawley	M	P21-P70	P73	EPM	no	%Percentage open arm time	SEM	15.93	11.02	8	44.33	9.01	8
Shangase KB 2024	Rat-Sprague Dawley	M	62 days	P78,P79	EPM	yes	%Percentage open arm time	SEM	60.69	5.1	8	37.99	6.95	8

Table 2. Studies on OFT

Reference/Year	Species tested	Sex	Format of separation	Age of testing	Test	Injection	text time(min)	Data	Variance Measure	SI			GH		
										mean	Vm	n	mean	Vm	n
Yu-Chun Wang 2012	Rat-Wistar	M	P28-84	P91	OFT	no	10,20,30min	total distance(cm)	SEM	13.79	1.94	8	9.28	1.62	8
Maria Danet S. Lapiz 2000	Rat-Lister	M	P21	P49	OFT	yes	10min	total distance(cm)	SEM	41.33	4.95	12	35.76	6.99	12
Qingxuan Meng 2010	Rat-Sprague-Dawley	M	P21-49	P76	OFT	no	10min	center(s) total distance(cm)	SEM	44.55	8.48	16	38.57	7.98	16
ANNETTE DOMENEY 1998	Rat-Wistar	M	P21-105	P105	OFT	yes	10,20,30min	total distance(cm)	SEM	28.47	2.52	10	17.33	3.62	10
I.C.Weiss 1999	Rat-Wistar	M	P21		OFT	no	10,20,30min	total distance(cm)	SEM	33.48	4.74	20	22.20	7.58	19
Mengdie Li 2024	Mice-Henan Province Skbeth Biotechnology Co., LTD, China	M,F	P21-P56	P70	OFT	yes	10	total distance(m)	SEM	74.48	2.76	15	28.97	2.75	15

Table 3. Studies on PPI

Reference/Year	Species tested	Sex	Format of separation	Age of testing	Test	Injection	Vm	SI									n	GH									n
								low			medium			high				low			medium			high			
								PPI%	SD	Vm	PPI%	SD	Vm	PPI%	SD	Vm		PPI%	SD	Vm	PPI%	SD	Vm	PPI%	SD	Vm	
ANNETTE DOMENEY 1998	Rat-Wistar	M	P21-105	P105	PPI	no	SEM	-4.77	19.07	3.74	8.17	0.82	0.26	7.66	2.43	0.77	10	12.85	13.47	4.26	32.26	22.58	7.14	37.02	30.42	9.62	10
								.	.	.	.	.	.	21.02	18.02	5.7	10	.	.	.	.	.	.	49.11	26.63	8.42	10
Bart A. Ellenbroek* 2002	Rat-Wistar	M,F	P9 P13	P69	PPI	no	SEM	26.53	25.25	7.29	54.88	17.49	5.05	69.19	15.55	4.49	12	22.74	17.94	4.35	34.95	24.29	5.89	52.63	20.24	4.91	17
Bartlomiej Lukasz 2013	Rat-Wistar	M	P25-P84	P60,80	PPI	no	SEM	60.72	15.72	5.24	65.96	1.65	0.55	62.17	16.26	5.42	9	61.99	15.18	5.06	65.78	15.72	5.24	73.92	16.08	5.36	9
								.	.	.	.	.	.	62.17	23.31	7.77	9	.	.	.	.	.	.	79.88	13.56	4.52	9
Chih-Yuan Ko2015	Rat-Sprague-Dawley	M,F	P21-P86	.	PPI	yes	SEM	8.84	21.96	6.34	26.71	25.70	7.42	.	.	.	12	29.21	12.16	3.51	46.75	13.54	3.91	.	.	.	12
								22.93	23.83	6.88	.	.	.	.	.	.	12	35.21	19.16	5.53	.	.	.	.	.	.	12
Elisabeth B. Binder 2001	Rat-Long–Evans	F	P23	.	PPI	yes	SEM	24.26	15.05	2.38	39.45	17.77	2.81	.	.	.	40	37.06	13.47	2.13	56.21	9.42	1.49	.	.	.	40
								32.09	15.87	2.51	.	.	.	.	.	.	40	46.85	11.57	1.83	.	.	.	.	.	.	40
Ewelina Bator 2018	Rat-Wistar	M	P21	P45,70	PPI	yes	SEM	11.95	13.51	3.9	26.02	13.51	3.9	33.98	10.43	3.01	12	10.81	10.43	3.01	23.01	9.84	2.84	28.86	10.70	3.09	12
								.	.	.	.	.	.	40.08	13.51	3.9	12	.	.	.	.	.	.	37.07	13.23	3.82	12

G.B. Varty1995	Rat-Wistar	M	P21-77	P77	PPI	yes	SEM	-9	29.39	12	7	19.60	8	41	14.70	6	6	14	12.25	5	34	9.80	4	60	14.70	6	6
I.C.Weiss 1999	Rat-Wistar	M	P21	.	PPI	yes	SEM	5.02	22.39	4.57	18.53	22.09	4.51	28.85	23.03	4.7	24	6.73	22.78	4.65	19.63	21.21	4.33	28.53	21.41	4.37	24
.								.	.	.	.	.	.	36.64	24.15	4.93	24	.	.	.	.	.	.	46.45	23.71	4.84	24
J. R. T. GREENE 2001	Rat-Wistar	M	P21-77	P77	PPI	no	SEM	41.96	23.00	8.13	.	.	.	.	.	.	8	58.5	11.62	4.11	.	.	.	.	.	.	8
								28.47	59.85	21.16	.	.	.	.	.	.	8	67.93	13.60	4.81	.	.	.	.	.	.	8
								56.01	23.53	8.32	.	.	.	.	.	.	8	80.87	9.14	3.23	.	.	.	.	.	.	8
Katrine Fabricius 2010	Rat-Lister Hooded rats	F	P25-P84	P84	PPI	no	SEM	4.46	9.77	2.37	21.53	9.52	2.31	43	10.39	2.52	17	12.18	8.91	2.3	40.25	10.92	2.82	57.55	9.22	2.38	15
Laetitia Strauss 2013	Rat-Wistar	M	P21-77	P77	PPI	yes	SEM	7.68	9.23	2.92	11.77	13.19	4.17	16.42	14.10	4.46	10	25.27	7.84	2.48	29.69	8.89	2.81	32.29	9.01	2.85	10
								.	.	.	.	.	.	18.14	17.46	5.52	10	.	.	.	.	.	.	36.05	7.87	2.49	10
Lan Sun 2018	Rat-Sprague-Dawley	M	P21-56	P57	PPI	no	SEM	41.18	15.06	5.02	.	.	.	36.47	15.72	5.24	9	59.68	10.26	3.42	.	.	.	57.11	11.25	3.75	9
								53.05	20.52	6.84	.	.	.	.	.	.	9	72.3	5.13	1.71	.	.	.	.	.	.	9
Lan Sun 2021	Rat-Sprague-Dawley	M	P21-P35 P46	P55	PPI	yes	SEM	52.22	21.72	7.68	.	.	.	.	.	.	8	72.74	4.36	1.54	.	.	.	.	.	.	8
								67.75	4.55	1.61	.	.	.	.	.	.	8	76.07	7.35	2.6	.	.	.	.	.	.	8
M. L. FITZGERALD 2013	Rat-Sprague-Dawley	M	P21-77	P77	PPI	no	SEM	31.48	17.34	5.78	55.19	18.42	6.14	.	.	.	9	41.18	24.96	8.32	55.91	17.25	5.75	.	.	.	9
								46.07	17.13	5.71	.	.	.	.	.	.	9	62.32	13.26	4.42	.	.	.	.	.	.	9
Man Lia,b,c, 2018	Rat-Sprague-Dawley	M	P21	P56	PPI	yes	SEM	59.9	10.89	3.85	.	.	.	57.96	10.44	3.69	8	76.73	11.20	3.96	.	.	.	77.18	9.90	3.5	8
Marisa Möller 2011	Rat-Sprague-Dawley	M	P21-77	P77	PPI	yes	SEM	0.38	19.73	6.24	11.92	19.35	6.12	31.55	10.97	3.47	10	43.41	9.36	2.96	49.91	6.58	2.08	57.73	7.59	2.4	10
								.	.	.	.	.	.	40.25	10.37	3.28	10	.	.	.	.	.	.	64.1	5.79	1.83	10
Marisa Möller 2013	Rat-Sprague-Dawley	M	P21-77	P77	PPI	yes	SEM	0.53	2.06	0.65	7.11	5.60	1.77	15.79	6.23	1.97	10	37.04	16.03	5.07	48.09	7.91	2.5	59.08	9.14	2.89	10
								.	.	.	.	.	.	25	8.54	2.7	10	.	.	.	.	.	.	68.68	7.30	2.31	10
Mark A.1993	Rat-Lister Hooded ratsRat-Sprague-Dawley	M	P20-	.	PPI	no	SEM	20.34	29.92	10.58	.	.	.	30.51	62.11	21.96	8	27.8	38.64	13.66	.	.	.	67.93	10.75	3.8	8
								-12.07	48.31	17.08	.	.	.	.	.	.	8	21.56	29.92	10.58	.	.	.	.	.	.	8
								34.44	23.79	8.41	.	.	.	.	.	.	8	62.1	13.04	4.61	.	.	.	.	.	.	8
Nurith Amitai 2013	Rat-Long-Evans Hooded	M	P24-80	P80	PPI	no	SEM	9.94	26.16	5.13	45.71	23.66	4.64	.	.	.	26	17.89	26.28	4.88	63.27	21.43	3.98	.	.	.	29
								21.28	24.53	4.81	.	.	.	.	.	.	26	36.94	42.33	7.86	.	.	.	.	.	.	29
Philip LR 2014	Rat-Lister Hooded rats	M	P23-65	P56	PPI	yes	SEM	.	.	.	16.4	22.25	6.71	28.85	9.88	2.98	11	.	.	.	24.14	27.46	8.28	40.05	20.66	6.23	11
								.	.	.	.	.	.	53.42	10.25	3.09	11	.	.	.	.	.	.	57.43	17.05	5.14	11
Roberta Andrejew 2021	Rat-Wistar	M	P21-77	P77	PPI	yes	SD	0.66	3.52	3.52	3.62	6.46	6.46	9.63	8.96	8.96	10	-0.97	5.55	5.55	13.7	10.14	10.14	24.09	8.51	8.51	9
Susan B 2002	Rat-Long–Evans hooded	M,F	P23	Male2,5,7W Female 4W	PPI	no	SEM	25.05	17.26	3.86	45.42	11.18	2.5	.	.	.	20	35.19	10.46	2.34	53.15	11.18	2.5	.	.	.	20
								35.84	12.97	2.9	.	.	.	.	.	.	20	44.86	######	42.16	.	.	.	.	.	.	20
Susan B. Powell a, c 2015	Rat-Sprague-Dawley	M,F	P24	8,2□	PPI	no	SEM	26.49	126.03	32.54	63.96	266.77	68.88	.	.	.	15	44.03	14.59	4.4	76.79	11.87	3.58	.	.	.	11
								30.75	157.51	40.67	.	.	.	.	.	.	15	57.16	11.41	3.44	.	.	.	.	.	.	11
Vaishali P 1998	Rat-Sprague-Dawley	M	P21-77	P77	PPI	yes	SEM	33.49	10.63	3.76	54.54	15.27	5.4	.	.	.	8	51.33	17.48	6.18	73.24	14.59	5.16	.	.	.	8
								47.57	13.29	4.7	.	.	.	.	.	.	8	63.22	14.62	5.17	.	.	.	.	.	.	8
VAISHALI P 1999	Rat-Sprague-Dawley Rat-Lister Hooded rats	M	P21-59	P59-91	PPI	no	SEM	14.95	110.39	21.65	47.77	260.92	51.17	.	.	.	26	18.3	92.44	22.42	61.94	######	66.18	.	.	.	17
								35.92	210.39	41.26	.	.	.	.	.	.	26	53.33	######	57.94	.	.	.	.	.	.	17
Yu-Chun Wang 2012	Rat-Wistar	M	P28-84	P91	PPI	no	SEM	.	.	.	26.36	102.98	36.41	42.01	137.09	48.47	8	.	.	.	42.73	######	53.36	64.2	######	70.59	8
Mengdie Li 2024	Mice-Henan Province Skbeth Biotechnology Co., LTD, China	M,F	P21-P56	P76	PPI	yes	SEM	.	.	.	.	.	.	0.65	0.04	.	12	.	.	.	.	.	.	0.91	0.03	.	12
Gideon Opeyemi Ayilara 2024	Mice- BALB/c	M,F	P21-P56	P57-P60	PPI	no	SEM	.	.	.	.	.	.	63.11	3.64	.	5	.	.	.	.	.	.	84.68	3.64	.	5

Table 4. Studies on MWM

Reference/Year	Species tested	Sex	Format of separation	Age of testing	Test	Injection	Data	Vm	SI			GH		
									mean	Vm	n	mean	Vm	n
Bartlomiej Lukasz 2013	Rat-Wistar	M	P25-P84	P60,80	no	Water maze	1-4 Escape incubation period/length of stay in a particular quadrant on day 5	SEM	14.67	1.87	9	11.68	1.87	9
M. D. S. Lapiz 2003	Rat-Lister Hooded rats	M	P21 6-8W		yes	Water maze	1-4 Escape incubation period/length of stay in a particular quadrant on day 5	SEM	16.22	2.66	5	17.85	3.68	5
Mengdie Li 2024	Mice-Henan Province Skbeth Biotechnology Co., LTD, China	M,F	P21-P56	P80	MWM	yes	1-4 Escape incubation period/length of stay in a particular quadrant on day 5	SEM	39.3	3.5	15	16.14	2.1	15
Ahmed M. Abdelfattah 2023	Rat-Wistar	M,F	P21-P84	P87	MWM	no	percentage of time spent in target quadrant (during probe test)	SEM	21.97	3.28	12	49.51	4.92	12

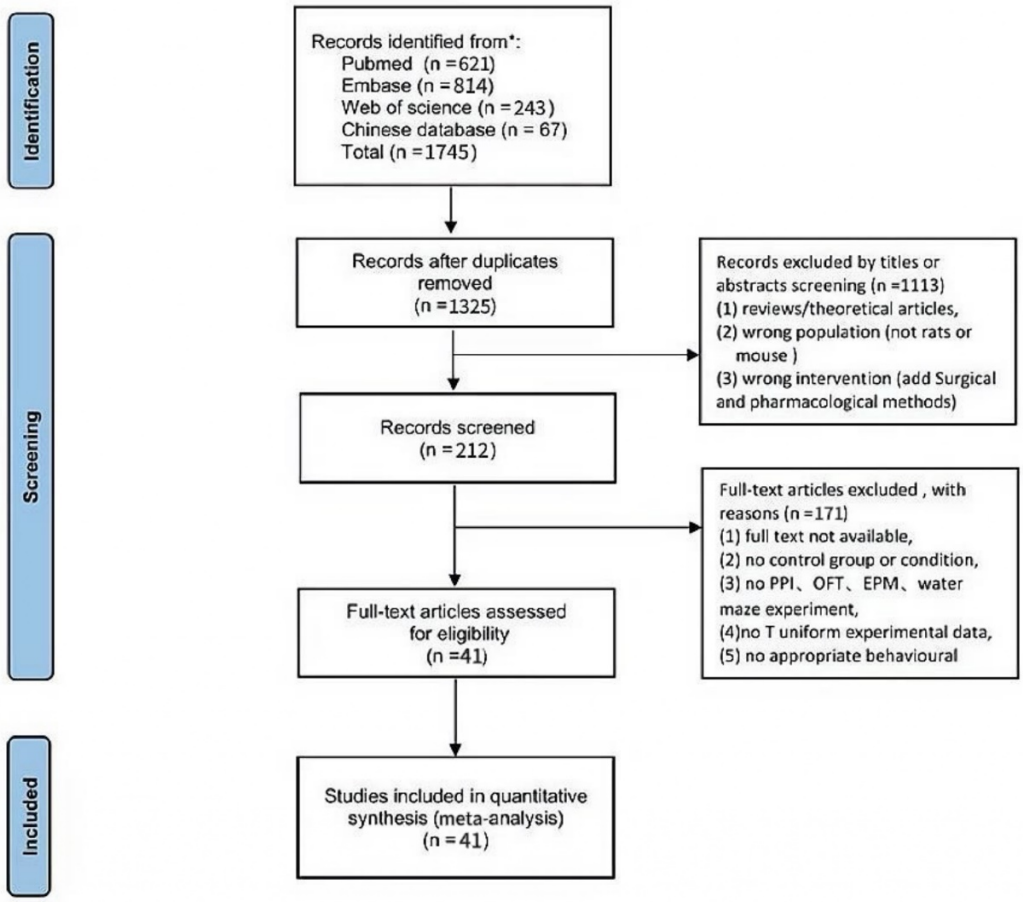

Figure 1. PRISMA flow-diagram of the study selection process for the meta-analysis

In the rats group, it (Figure 5) shows the forest plot for PPI(66-70 low), PPI(71-76 medium) and PPI(77- high) SDs with 95% confidence intervals and a summary mean difference showing average reductions of PPI(66-70 low) (95% CI=-0.63(-0.76, -0.05), p<0.00001) PPI(71-76 medium) (95% CI=-0.63(-0.80, 0.46), p < 0.00001) and PPI(77- high) (95% CI=-0.72(-0.92, -0.53), p < 0.0001) with SI when compared with healthy controls. The heterogeneity across studies was substantial for both PPI (66-70 low) (I^2 =57%, Chi^2=86.5, df=37), PPI (71-76 medium) (I^2=77%, Chi^2=86.50, df=20) and PPI (77- high) (I^2=80%, Chi^2=112.63, df=22).

MWM: The MWM experiment, which included five articles (18,20,32,44,45] with a total of 96 subjects, described the use of the MWM to examine the effects of social isolation rearing on learning and memory function in schizophrenia-like behavior (Figure 6). In MWM, the overall effect of social isolation rearing was significant (95% confidence interval=0.97 (0.31, 1.62), Z=2.90, p=0.004), and inter-study heterogeneity was significant (I^2=96%, χ^2=91.55, df=4).

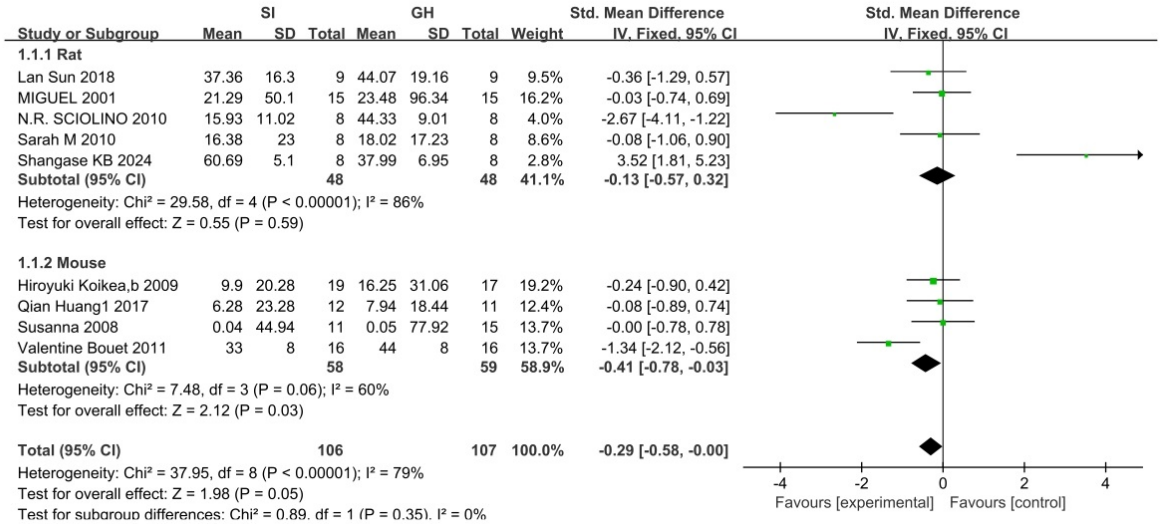

Figure 2. EPM forest plot

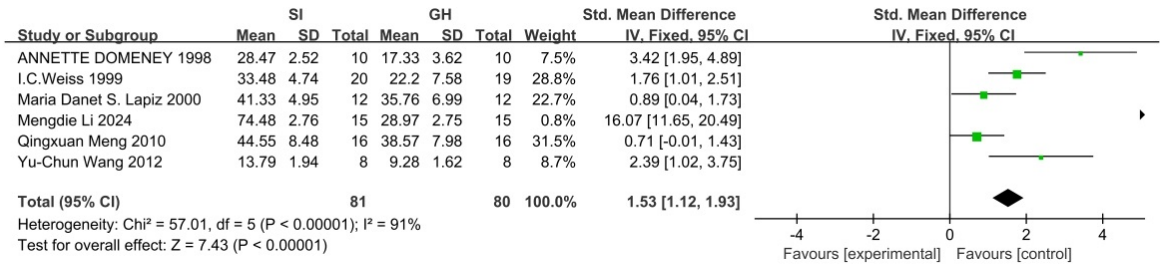

Figure 3. OFT forest plot

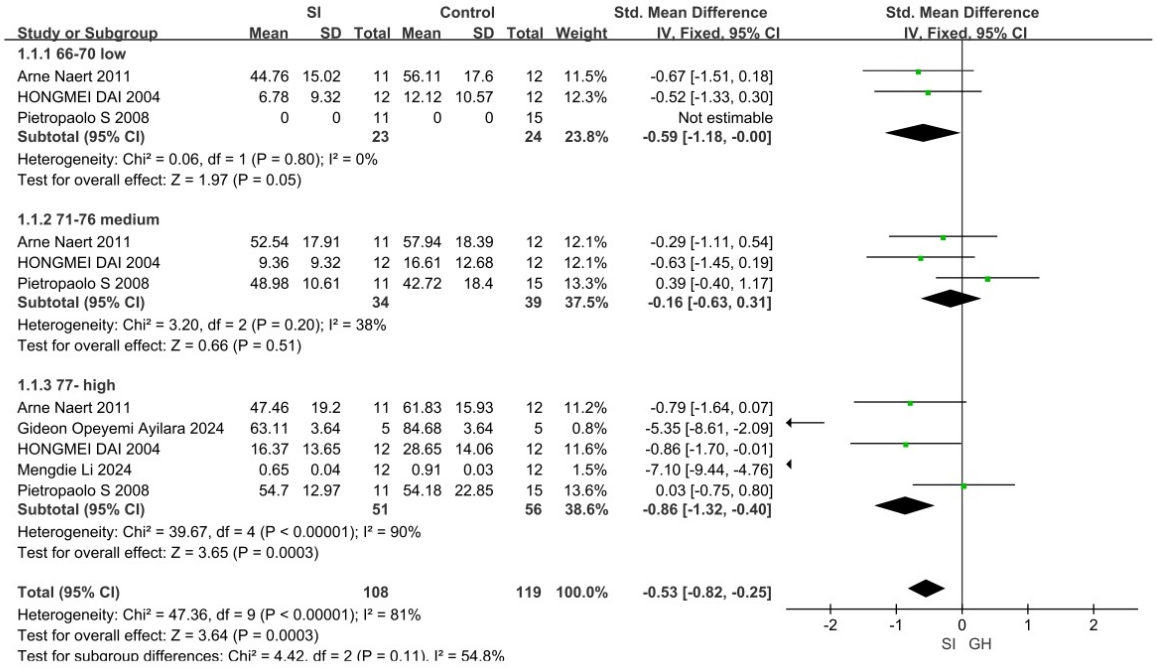

Figure 4. PPI forest plot for mice

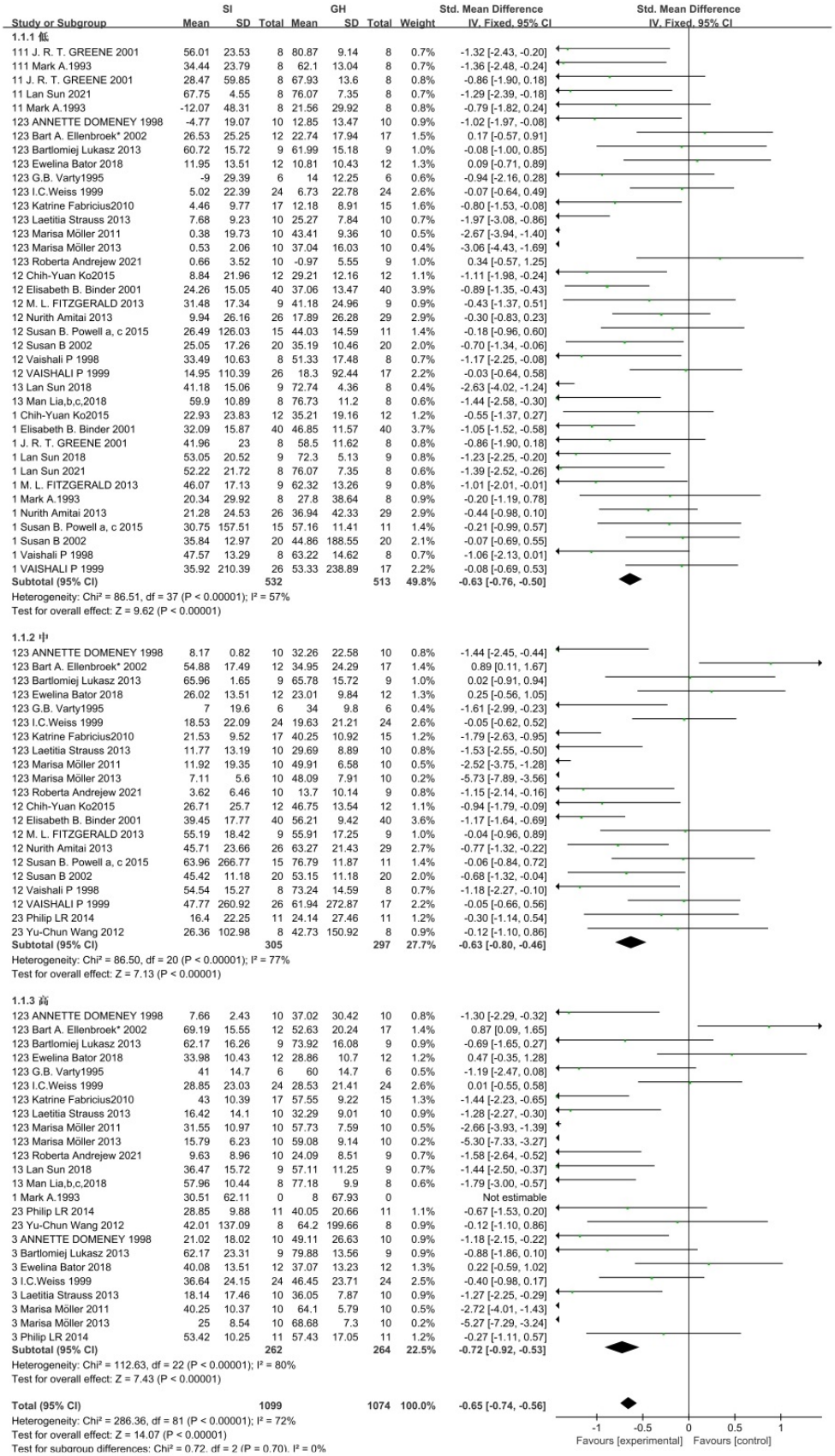

Figure 5. PPI forest plot for rats

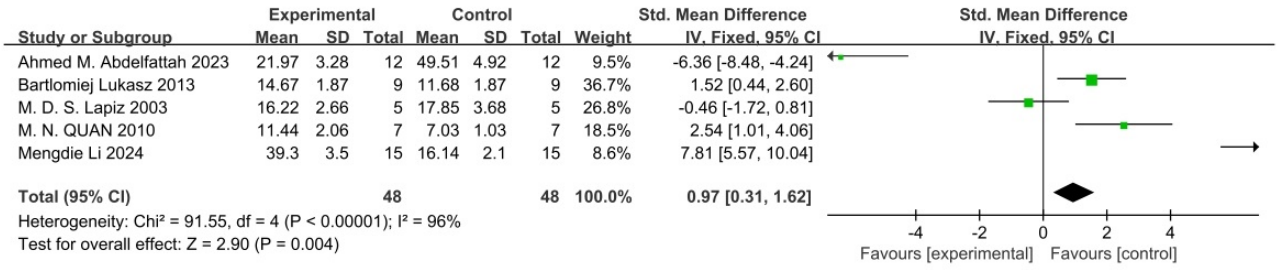

Figure 6. MWM forest plot

Discussion

Meta-analyses of animal data have become increasingly relevant over the last few years, which not only help researchers understand the pathogenesis of diseases, but also provide a testing platform for new treatment programs. To the best of our knowledge, this study represents the first systematic review and meta-analysis investigating the impact of social isolation on schizophrenia-like behavior in rodents.

In recent years, some studies have investigated the effect of social isolation rearing on the rodents of schizophrenia-like behavior have reported various effects, which in general are promising. But we have not been able to state which are the overall effects of social isolation rearing on schizophrenia-like behavior and in which social isolation rearing in animal models is able to produce an unambiguous increase in schizophrenia-like behavior.

We found that the social isolation rearing is strongly associated with anxiety behavior, exploratory behavior, cognitive and sensory impairments and learning and memory function (i.e., The main behavioral symptoms of schizophrenia). These schizophrenic-like behaviors tended to increase in the social isolation rearing group compared with control animals (Figures 2-5). The publication bias was assessed using a funnel plot, indicating marginal effect of publication bias mostly due to small sample size or inadequate reports of negative data. However, most studies were distributed in a funnel-shaped area of the plot.

However, Findings were consistent in sensitivity analyses but there was noted to be a large amount of statistical heterogeneity. This suggests that different research groups have trouble reproducing schizophrenia-like behavior (Figures 3-6). Especially, Matar, et al. [46] and colleagues highlighted that a heterogeneous response may confirm the validity of animal studies because humans do not clearly respond homogeneously to potentially traumatic experiences [46]. In the present study, the overall outcome of the high heterogeneity data had a large effect on exacerbating schizophrenia-like behavior, possibly related to differences in social isolation parenting time and inconsistent behavioral experimental operations. While some studies reported schizophrenia-like behaviors results induced by social isolation rearing, others reported increased schizophrenia-like behaviors. Therefore, we needed to explore the sources of heterogeneity and obtained more accurate results. Although, Injection behavior had widely varying effects on biological processes and behavior, we included them considering the fact that most articles contained them and the comprehensiveness of the results.

Due to the limited data sample, we only performed interspecific analyses of EPM and PPI. We only found rodent strain differences in the anxiety are prominent in the literature in EPM. In this meta-analysis, it was evident that there was no significant statistical significance in schizophrenic behavior between the mice after social isolation rearing and the control group ($p > 0.05$). In the PPI experiment, there was no significant difference between rats and mice. In the subgroup analysis of PPI, compared with the experimental group and the control group, there is a higher difference in the decibels in the middle, which indicates that under the decibels above 66-70 dB and 77 dB, social isolation rearing has A greater impact on cognitive and sensory impairments (A type of schizophrenic behavior). Altogether, discrepancies among these studies may be a result of varying isolation procedures (different onsets and durations), differing in experimental conditions (more anxiogenic or less), differing in age when tested, as well as strain and sex differences [47]. A number of articles refer to schizophrenia-like behaviors differences after gender is bred for social separation. Some study findings are contrary to a similar study using Swiss–Kunming mice, which revealed a male-preferentially decreased despair behavior in isolated groups. Another study found that male but not female-isolated-reared rats exhibited a higher percentage of time in open arms of EPM compared with their group-reared controls [47].

A number of limitations of the research included in this Meta-analysis should be acknowledged. Firstly, due to the limited number of publications, the funnel plot shows bias, suggesting that more high-quality studies should be included. Secondly, although the database has been carefully and comprehensively searched, there are still few studies selected for each behavioral blood type, which can lead to bias. Aside from the abovementioned speculations, several limitations should be noted. The data derived using digital software were different from the actual study results, so there was a certain degree of data error. In addition, our meta-analysis checked only rodents and it was unknown what social isolation rearing did in other animals. Future research should target such limitations.

Conclusion

This meta-analysis confirms that post-weaning social isolation rearing induces robust schizophrenia-like behavioral deficits in rodents, manifested as hyperactivity in OFT, anxiety-like responses in the EPM, and sensorimotor gating impairments in PPI. The observed effects demonstrate significant strain-dependent heterogeneity, underscoring the necessity for standardized protocols with extended isolation durations (> 12 weeks) and multi-domain behavioral assessments in future studies. Researchers should prioritize isolation paradigms aligned with specific schizophrenia endophenotypes to optimize translational validity.

CRediT authorship contribution statement

Minyue Zhang: Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Wanqi Jin: Writing–review & editing, Writing–original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. Yumu Guo: Supervision,

Data curation. Chunyue Huo: Validation, Supervision, Project administration, Conceptualization.

Conflicts of interest

The authors declare that no actual or potential conflicts of interest exist, including any financial, personal, or other relationships with other people or organizations.

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Availability of data and materials

The datasets generated and analyzed during the current study are publicly available.

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