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ORIGINAL INVESTIGATION

Behavioral and transcriptional effects of repeated electroconvulsive seizures in the neonatal MK-801-treated rat model of schizophrenia

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Abstract

Rationale Electroconvulsive therapy (ECT) is an effective treatment modality for schizophrenia. However, its antipsychotic-like mechanism remains unclear.

Objectives To gain insight into the antipsychotic-like actions of ECT, this study investigated how repeated treatments of electroconvulsive seizure (ECS), an animal model for ECT, affect the behavioral and transcriptomic profile of a neurodevelopmental animal model of schizophrenia.

Methods Two injections of MK-801 or saline were administered to rats on postnatal day 7 (PN7), and either repeated ECS treatments (E10X) or sham shock was conducted daily from PN50 to PN59. Ultimately, the rats were divided into vehicle/sham (V/S), MK-801/sham (M/S), vehicle/ECS (V/E), and MK-801/ECS (M/E) groups. On PN59, prepulse inhibition and locomotor activity were tested. Prefrontal cortex transcriptomes were analyzed with mRNA sequencing and network and pathway analyses, and quantitative real-time polymerase chain reaction (qPCR) analyses were subsequently conducted.

Results Prepulse inhibition deficit was induced by MK-801 and normalized by E10X. In M/S vs. M/E model, *Egr1*, *Mmp9*, and *S100a6* were identified as center genes, and interleukin-17 (IL-17), nuclear factor kappa B (NF-κB), and tumor necrosis factor (TNF) signaling pathways were identified as the three most relevant pathways. In the V/E vs. V/S model, mitophagy, NF-κB, and receptor for advanced glycation end products (RAGE) pathways were identified. qPCR analyses demonstrated that *Igfbp6*, *Btf3*, *Cox6a2*, and *H2az1* were downregulated in M/S and upregulated in M/E.

Conclusions E10X reverses the behavioral changes induced by MK-801 and produces transcriptional changes in inflammatory, insulin, and mitophagy pathways, which provide mechanistic insight into the antipsychotic-like mechanism of ECT.

Keywords Electroconvulsive therapy · Schizophrenia · Immediate early genes · Nuclear factor-κB · Insulin signaling · Mitophagy

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Introduction

Electroconvulsive therapy (ECT) is a treatment modality for various neuropsychiatric disorders, including depression and schizophrenia (Lisanby 2007; Weiner and Reti 2017). ECT is a safe and effective adjunct to antipsychotic therapy for patients with treatment-resistant schizophrenia (de Mangoux et al. 2022; Kim et al. 2018a; Petrides et al. 2015; Sanghani et al. 2018; Sinclair et al. 2019; Youn et al. 2019). ECT is particularly effective in patients with schizophrenia who exhibit catatonia or suicidal behaviors (Grover et al. 2019). This treatment can prevent relapse in schizophrenia without significant adverse effects and may improve social functioning and quality of life (Grover et al. 2019; Ward et al. 2018; Youn et al. 2019). Evidence strongly indicates that ECT has not only antidepressant but also antipsychotic effects (Ali et al. 2019; Kim et al. 2018a; Petrides et al. 2015; Sinclair et al. 2019; Ward et al. 2018), and it has become a crucial part of current clinical guidelines for the management of schizophrenia (Galletly et al. 2016; Grover et al. 2017; Lee et al. 2020).

Animal models of in vivo genetic and molecular mechanisms are a useful tool to understand the mechanism of action of ECT. Repeated treatments of electroconvulsive seizure (ECS), an animal model for ECT, induce neurogenesis, synaptic modifications, dendritic remodeling, increased spine density, increased expression of neurotrophic factors, alterations in the activity of intracellular signaling molecules, and anti-apoptotic activity (Enomoto et al. 2017; Maffioletti et al. 2021; Meyers et al. 2023; Segi-Nishida 2011; Tartt et al. 2023). Moreover, repeated ECS treatments alter the expression levels of genes related to neurotransmission and neural plasticity (Chang et al. 2018; Huang and Chen 2008; Kobayashi and Segi-Nishida 2019). However, most studies to date have been designed to examine the antidepressant activity of ECT (Maffioletti et al. 2021). The mechanisms underlying the antipsychotic action of ECT require further investigation.

The N-methyl-D-aspartic acid (NMDA) glutamate receptor hypofunction hypothesis is a leading theory for understanding the pathophysiology of schizophrenia (Bygrave et al. 2019; Kantrowitz and Javitt 2010; Nakazawa and Sapkota 2020). Neurodevelopmental animal models exhibit behavioral and molecular alterations compatible with schizophrenia (Bialon and Wasik 2022). Neuronal and synaptic development, myelination, and gliogenesis are most pronounced around postnatal day 7 (PN7), which is analogous to the third trimester of pregnancy in humans (Bolon et al. 2021; Semple et al. 2013). In this period, susceptibility to the apoptotic effects of NMDA receptor antagonism is high (Lim et al. 2012a; Ritter et al. 2002), which can cause defects in dopamine regulation and parvalbumin neuron maturation, subsequently producing schizophrenia-like phenotypes (Abekawa et al. 2007; Belforte et al. 2010; Nakazawa et al. 2017). Administration of MK-801, a selective non-competitive NMDA receptor antagonist (Tricklebank et al. 1989), during this critical period, induces long-term behavioral and cognitive changes in rodents, such as decreased prepulse inhibition of acoustic startle responses and impairments in spatial memory (Lim et al. 2012a; Mohammadi et al. 2020; Uehara et al. 2009; Uttl et al. 2018). MK-801 injections during the neonatal period provide a useful neurodevelopmental animal model, especially for evaluating antipsychotic-like activity (Niu et al. 2020).

The present study was performed to examine the behavioral and transcriptomic changes that underlie the antipsychotic mechanism of ECT using the MK-801 model of schizophrenia. We previously reported that neonatal MK-801 treatment induces dysregulations in protein translation signal pathways in the prefrontal cortex (PFC) of developing rats (Kim et al. 2010a). In this study, the neonatal NMDA receptor antagonist was administered as in our previous study (Kim et al. 2010a), and long-term behavioral changes were evaluated during the young adult period. The PFC is one of the central brain regions of antipsychotic action (Artigas 2010; MacDonald et al. 2005), and we conducted mRNA sequencing, network, and pathway enrichment analyses of PFC samples. Quantitative real-time polymerase chain reaction (qPCR) was then conducted to confirm the findings. We demonstrated that repeated ECS treatments restored the behavioral abnormalities and induced transcriptomic changes in the PFC.

Methods

Animals

All animals in this study were treated in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. The experiment was approved by the animal subjects review board of Seoul National University Hospital. Female Sprague–Dawley rats (weighing 12–16 g) were housed with their mother under a 12-h light/12-h dark cycle with food and water available ad libitum. Female rats were chosen for their more conspicuous long-term behavioral changes in response to neonatal MK-801 treatment (Kim et al. 2010a).

Experimental procedure

This study was designed to examine the effects of repeated treatments of ECS on the long-term behavioral and cortical transcriptional changes induced by neonatal MK-801

treatment. On PN7, the rats were randomly injected with either MK-801 or vehicle (normal saline). The rats were housed with their dam until weaning on PN21. On PN50, each group was randomly divided into two subgroups and treated daily with either ECS (E10X) or sham shock (sham) for 10 days. Ultimately, the rats were divided into four subgroups: vehicle/sham (V/S), MK-801/sham (M/S), vehicle/E10X (V/E), and MK-801/E10X (M/E). After the last ECS or sham treatment, a prepulse inhibition (PPI) test and locomotor activity assessment were performed on PN59. The rats were decapitated 24 h after the last ECS or sham treatment, and the PFC was dissected and used for mRNA sequencing, network and pathway enrichment analyses, and qPCR analyses. The experimental design is summarized in Fig. 1.

MK-801 treatment

MK-801 was administered as in our previous study (Kim et al. 2010a). We administered subcutaneous injections of either normal saline vehicle or 1.0 mg/kg MK-801 (Tocris Bioscience, Bristol, UK) dissolved in normal saline to the rats on PN7, which is within the period of high vulnerability to MK-801 (Lim et al. 2012a; Ritter et al. 2002). Among the MK-801 treatment conditions of our previous report, the protocol of two 1.0 mg/kg MK-801 injections administered 8 h apart was selected because it resulted in the most prominent molecular changes in the frontal cortex (Kim et al. 2010a). Drug injections were performed outside the cage under a heating lamp, and the pups were returned to the cage immediately after the injections.

ECS treatment

From PN50, rats that had been treated with MK-801 or vehicle on PN7 were divided into the sham group (sham shock for 10 days) and the E10X group (ECS for 10 days). Both groups were treated daily at the same time (12:00–13:00) for 10 days. As previously reported (Kim et al. 2022), ECS was administered to the rats using ear-clip electrodes and a pulse generator (UgoBasile ECS Unit-57800–001; UgoBasile, VA, Italy) at a frequency of 100 pulses/s, with a pulse width of 0.5 ms, shock duration of 0.5 s, and current of 55 mA. These parameters were comparable to protocols of other ECS studies on psychosis model rodents (Kimura et al. 2021; Limoa et al. 2016) and settings used in clinical ECT on patients (Galletly et al. 2014; Minelli et al. 2016). Sham-treated control animals were handled in the same fashion as ECS-treated animals, but no electric current was delivered. ECS-induced seizure was validated by observing general convulsions consisting of tonic and clonic phases, and the duration of the convulsions was measured. ECS-treated animals that experienced a generalized convulsion for more than 30 s were included for further analysis.

Measurement of PPI

The PPI testing protocol used in this experiment was based on that described in previous studies (Gururajan et al. 2011; Lim et al. 2012b) with minor modifications. All rats were first acclimatized to the enclosure in the startle chamber on PN58 and exposed only to background noise (65 dB) for 30 min. On PN59, each rat underwent a PPI test of a 5-min acclimatization period (65-dB background sound) and subsequent 120-dB startling pulses of 40-ms duration that were presented with or without prepulses. The non-startling prepulses were 3, 6, or 12 dB above the background and 20 ms in duration, with an inter-stimulus interval (start of prepulse to start of pulse) of 100 ms. Background- and prepulse-only trials were also completed. Each trial type was completed 10 times in a pseudorandom order with an average inter-trial interval of 15 s. In addition, six pulse alone trials were presented at the start and end of each session. The startle magnitude was determined by taking the average of 100 1-ms samples of accelerometer startle responses immediately following the onset of the pulse. Percent PPI was computed as

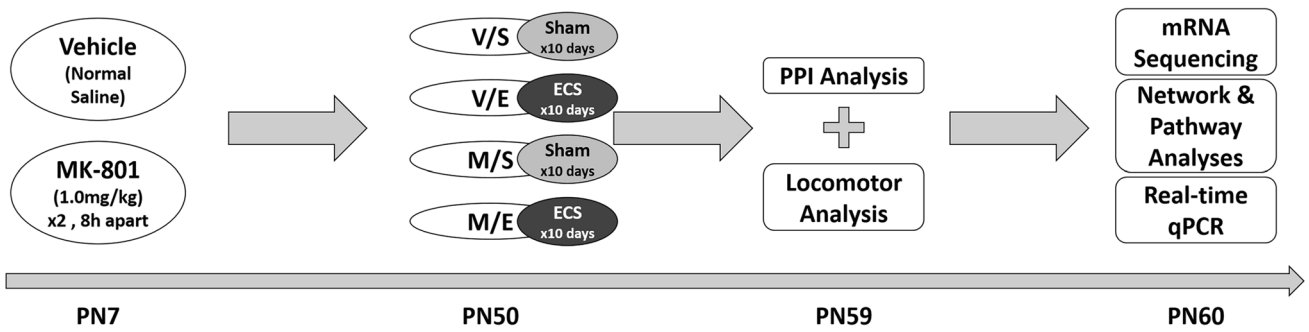

Fig. 1 Schematic outline of the experimental design. The schematic illustrates the ages of the animals and treatments applied in each group. Abbreviations: V/S, vehicle-sham shock × 10 days (Sham) group; V/E, vehicle-ECS × 10 days (E10X) group; M/S, MK-801-Sham group, M/E, MK-801-E10X group; PN, postnatal day; PPI, prepulse inhibition; qPCR, quantitative polymerase chain reaction

[1 – (mean startle magnitude after prepulse and pulse/mean startle magnitude after pulse alone)] × 100.

Measurement of locomotor activity

Locomotor activity was measured with video tracking software (Activity Monitor 5; MED Associates, St. Albans, VT, USA), and locomotor activity was measured during the light phase of the day (12:00–20:00) as previously reported (Kim et al. 2013, 2008). The rats were acclimated to the testing environment 1 day before the test, and the distance traveled in 30 min was measured.

RNA isolation

On PN60, the rats were decapitated, and fresh frozen brain tissue was obtained. We defined the PFC as the cortical tissues located rostrally to the genu of the corpus callosum. The PFC was dissected and analyzed using a QuantSeq 3' mRNA sequencing kit (Lexogen, Vienna, Austria). Total RNA was isolated using a Trizol reagent (Invitrogen, Waltham, MA, USA). RNA quality was assessed by Agilent 2100 Bioanalyzer using the RNA 6000 Nano Chip (Agilent Technologies, Santa Clara, CA, USA), and RNA quantification was performed using ND 2000 Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

Library preparation and sequencing

The library of control and test RNAs was constructed using QuantSeq 3' mRNA-Seq Library Prep Kit (Lexogen) according to the manufacturer's instructions. In brief, 500 ng total RNA was prepared, an oligo-dT primer containing an Illumina-compatible sequence at its 5′ end was hybridized to the RNA, and reverse transcription was performed. After degradation of the RNA template, second strand synthesis was initiated by a random primer containing an Illumina-compatible linker sequence at its 5′ end. The double-stranded library was purified by using magnetic beads to remove all reaction components. The library was amplified to add the complete adapter sequences required for cluster generation. The finished library was purified from PCR components. High-throughput sequencing was performed as single-end 75-bp sequencing using a NextSeq 500 system (Illumina, San Diego, CA, USA).

Transcriptomic analyses

QuantSeq 3′ mRNA-Seq reads were aligned using Bowtie 2 (SourceForge, San Diego, CA, USA) (Langmead and Salzberg 2012). Bowtie 2 indices were generated from either the genome assembly sequence or the representative transcript sequences for alignment to the genome and transcriptome. The alignment file was used for assembling transcripts, estimating their abundances, and detecting differential expression of genes. Differentially expressed genes (DEGs) were determined based on counts from unique and multiple alignments using coverage in BEDTools (SourceForge) (Quinlan et al. 2010). The read count data were processed based on the quantile normalization method using edgeR in the R environment (R Development Core Team, 2016) via Bioconductor (Gentleman et al. 2004). Gene classification was based on searches of the DAVID database (https://david-d.ncifcrf.gov/) and Medline database (https://www.ncbi.nlm.nih.gov/).

Network and pathway analyses

DEGs that met the following criteria were considered for the network analysis: false discovery rate (FDR) of < 0.05 in the model that compared all four groups separately as well as in the model of interest, and an absolute value of log2 value of fold change (log2FC) of > 0.5. Gene regulatory networks in these DEGs were discovered via NetworkAnalyst with reference to SIGnaling Network Open Resource 2.0 (SIGNOR 2.0). Only the subnetworks with the most nodes were analyzed. The resulting interactome depicted a subnetwork that maximally connected the seeds (Zhou et al. 2019). The degree and betweenness distribution of nodes were calculated. To identify the relevant biological pathways, the identified DEGs were compared to the Kyoto Encyclopedia of Genes and Genomes (KEGG) database for enrichment analysis. Molecular pathways with at least 3 hits, a P-value < 0.0001, and an FDR of < 0.05 were included.

qPCR analyses

Among the identified DEGs, qPCR analysis was conducted on genes with a log2FC of > 1 or log2FC of < -1 and genes that code proteins with degree of ≥ 3 in the gene regulatory network. Genes with no corresponding human gene or no annotations in Ensembl were excluded. The analysis mostly followed previously described procedures (Park et al. 2014). Total RNA was extracted from the rodent PFC, and 1 µg of the total RNA was used to produce the corresponding complementary DNA using Superscript II Reverse Transcriptase (Invitrogen). Next, qPCR was performed using an ABI PRISM 7500 Real-Time PCR System (Applied Biosystems, Waltham, MA, USA) Relative amounts of mRNA were calculated by the comparative cycle threshold (Ct) method. The average fold change of each gene was normalized to the Ct value of beta-actin. The primer sequences for the qPCR analysis are shown in Supplementary Table 1.

Statistical analyses

At each prepulse stimulus intensity, PPI was analyzed by three-way analysis of variance (ANOVA) using drug and shock as the independent variables, followed by post hoc Tukey's test. Two-way ANOVA tests were conducted on locomotor activity and the qPCR results. All results are in means ± standard error of the mean (SEM). All statistical tests and corresponding graphs were generated using GraphPad Prism for Windows (ver. 10.0.1.; GraphPad Software, La Jolla, CA, USA), and *P*-values of < 0.05 were considered statistically significant.

Results

PPI assay

PPI deficit is a reliable behavioral phenotype in animal models of schizophrenia (Lim et al. 2012b; Zhao et al. 2013). Previous studies have reported that early postnatal administration of NMDA receptor antagonists in rodents induces PPI deficits in the adolescent and adult periods (Garcia-Mompo et al. 2020; Lim et al. 2012b). In this study, MK-801 or vehicle was injected into rats on PN7, and ECS or sham shock was then administered daily for 10 days (PN50-PN59). On PN59, PPI was measured to examine the psychotomimetic effects of early postnatal MK-801 in the young adult period and the effects of repeated ECS treatments. Three-way ANOVA demonstrated a significant main effect of E10X ($P = 0.049$, F (1, 20) = 4.400) and a significant interaction effect between E10X and MK-801 ($P = 0.049$, F (1, 20) = 4.385). A significant interaction effect between E10X and MK-801 ($P = 0.018$, F (1, 20) = 6.591) was observed at the prepulse stimulus intensity of 12 dB, whereas no such effect was found at 3 or 6 dB. Post hoc analyses demonstrated that at the prepulse stimulus intensity of 12 dB, the PPI value was significantly lower in M/S than in V/S ($P = 0.025$) and significantly higher in M/E than in M/S ($P = 0.033$) (Fig. 2a). These findings indicated that neonatal MK-801 treatment on PN7 induced PPI deficits in young adult rats and that these deficits were normalized by repeated ECS treatments.

Locomotor activity test

Locomotor activity is reportedly affected by early postnatal NMDA receptor antagonism; however, the findings have varied depending on the experimental conditions (Gururajan et al. 2011; Hlavacova et al. 2023; Li et al. 2023; Lim et al. 2012a). In this study, locomotor activity was tested on PN59 to elucidate the effects of neonatal MK-801 on locomotion and to determine whether repeated ECS treatments could normalize the MK-801-induced changes. The total distance traveled during the 30-min test session was 2350, 1415, 2217, and 1904 cm in V/S, M/S, V/E, and M/E, respectively. Two-way ANOVA revealed that E10X had a significant main effect on the locomotor activity of the rodents ($P = 0.003$, F (1, 48) = 10.068), while neonatal MK-801 treatment showed no significant main effect (Fig. 2b). Post hoc analyses revealed that the distance traveled was significantly shorter in V/E than in V/S ($P = 0.009$) and M/S ($P = 0.034$).

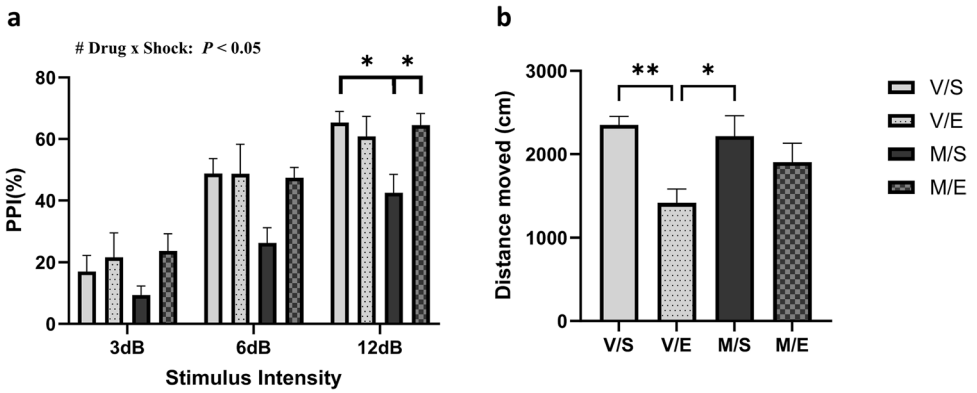

Fig. 2 Behavioral effects of MK-801 and repeated ECS treatments on rats. The figure shows **a** PPI and **b** locomotor activity of the animals. PPI (%) was calculated as percent of [1 − (mean startle magnitude after prepulse and pulse/mean startle magnitude after pulse alone)] × 100. PPI data were organized according to the prepulse stimulus intensity. Locomotor activity was measured as the distance moved in centimeters in an open field during a 30-min test session. Bars represent mean ± SEM of each behavioral assay. $*P < 0.05$ and $**P < 0.01$ (significant differences between groups). $\#P < 0.05$ (significant interactions between MK-801 treatment and electroconvulsive shock). Abbreviations: V/S, vehicle-sham shock × 10 days (Sham) group; V/E, vehicle-ECS × 10 days (E10X) group; M/S, MK-801-Sham group; M/E, MK-801-E10X group; PPI, prepulse inhibition; dB, decibels

Transcriptomic analyses of PFC samples

We used PFC samples from four animals in each group and obtained high-quality RNA (mean RNA integrity number: 8.7; range: 7.1–9.3) for mRNA sequencing analysis. With strict adherence to the procedures in the "Methods" section to ensure the quality of the mRNA, an average of 16,348,154 trimmed reads (SEM = 207,628) were processed to yield an average of 15,791,396 mapped reads per sample (SEM = 204,919) (Supplementary Table 2), to the reference genome, rn6, from the University of California, Santa Cruz genome database. The scatterplots of the gene expression levels between the two samples were drawn (Supplementary Fig. 1). A total of 17,048 genes were detected. The raw expression level results for each gene are also presented in the supplementary material.

In the analysis of the gene expression profile of M/E compared with M/S, performed to demonstrate the effect on neonatal MK-801-induced changes, 53 genes were identified as DEGs. The five most upregulated genes were *Crabp1*, *Mmp9*, *Sprr1a*, *Igfbp6*, and *Aqp1*, and the five most downregulated genes were *Harbi1*, *Fos*, *Fosb*, *Ptgds*, and *Egr2* (Table 1a, b). Next, the gene expression profile of V/E was compared with that of V/S to examine the effects of E10X. In total, 34 DEGs were identified. The five most upregulated genes were *Crabp1*, *Calml4*, *Aqp1*, *Timp1*, and *Masp1*, and

Table 1 Top five DEGs based on mRNA-Seq analysis ranked by fold change

Gene name	Ensembl gene ID	Log2FC	*P* value	FDR
(a) Upregulated in M/E, compared to M/S				
Crabp1	ENSRNOG00000023633	2.173655772	4.43E-19	1.65E-15
Mmp9	ENSRNOG00000017539	2.089660053	7.47E-08	4.19E-05
Sprr1a	ENSRNOG00000024028	1.769602671	9.90E-10	8.77E-07
Igfbp6	ENSRNOG00000010977	1.767518236	4.21E-06	1.37E-03
Aqp1	ENSRNOG00000011648	1.674059167	4.60E-08	2.95E-05
(b) Downregulated in M/E, compared to M/S				
Harbi1	ENSRNOG00000043204	− 1.722559975	1.52E-07	7.87E-05
Fos	ENSRNOG00000008015	− 1.326977137	2.96E-29	5.51E-25
Fosb	ENSRNOG00000046667	− 1.238502853	9.33E-14	1.58E-10
Ptgds	ENSRNOG00000015550	− 1.179094976	2.05E-07	9.52E-05
Egr2	ENSRNOG00000000640	− 1.09628899	5.40E-11	5.58E-08
(c) Upregulated in V/E, compared to V/S				
Crabp1	ENSRNOG00000023633	2.851953953	3.45E-13	6.43E-09
Calml4	ENSRNOG00000038202	2.524179642	5.24E-05	3.05E-02
Aqp1	ENSRNOG00000011648	1.812551855	1.00E-05	9.34E-03
Timp1	ENSRNOG00000010208	1.277733088	1.18E-05	9.98E-03
Masp1	ENSRNOG00000001827	0.953378862	2.90E-06	3.60E-03
(d) Downregulated in V/E, compared to V/S				
Cox6a2	ENSRNOG00000019851	− 1.263626858	7.70E-05	3.95E-02
Fos	ENSRNOG00000008015	− 1.088532153	1.61E-09	7.25E-06
Pdyn	ENSRNOG00000026036	− 1.023465337	9.75E-08	2.02E-04
Fosb	ENSRNOG00000046667	− 1.013057495	3.24E-06	3.78E-03
Egr4	ENSRNOG00000015719	− 1.006908967	6.84E-10	4.25E-06
(e) Upregulated in M/S, compared to V/S				
Mx2	ENSRNOG00000001963	2.464436765	4.19E-09	7.79E-05
Hspa2	ENSRNOG00000006472	0.665163188	4.21E-05	3.48E-02
(f) Downregulated in M/S, compared to V/S				
Igfbp6	ENSRNOG00000010977	− 2.273219315	2.08E-08	1.93E-04
Pde4a	ENSRNOG00000020828	− 1.641666343	1.41E-05	2.01E-02
H2az1	ENSRNOG00000010306	− 1.553003106	2.06E-06	4.26E-03
Btf3	ENSRNOG00000016912	− 1.548191245	1.28E-05	1.97E-02
Lmo2	ENSRNOG00000009401	− 1.080952282	4.99E-07	1.86E-03

(a) and (b) M/E versus M/S models, (c) and (d) V/E versus V/S models, and (e) and (f) M/S versus V/S models. For each gene, the Ensembl gene ID, log2FC, *P*-value, and FDR are listed. Abbreviations: *V/S*, vehicle-sham shock × 10 days (Sham) group; *V/E*, vehicle-ECS × 10 days group (E10X); *M/S*, MK-801-Sham group; *M/E*, MK-801-E10X group

the five most downregulated were *Cox6a2*, *Fos*, *Pdyn*, *Fosb*, and *Egr4* (Table 1c, d). Finally, the gene expression profile of M/S was compared with V/S to investigate the long-term effects of neonatal MK-801 treatment, and 16 DEGs were identified. The two upregulated genes were *Mx2* and *Hspa2*, and the five most downregulated genes were *Igfbp6*, *Pde4a*, *H2az1*, *Btf3*, and *Lmo2* (Table 1e, f). The complete list of DEGs and their respective log2FC, *P* value, and FDR are shown in Supplementary Table 3.

Network analyses of the transcriptomic data

We then produced a gene regulatory network of co-expressed genes using the transcriptomic data for each set of DEGs (see Methods section). In the network of DEGs of M/E compared with those of M/S, the *NfKb-p65/p50* complex was found to be located in the center and connected to *Egr1*, *S100a6*, and *Mmp9* (Fig. 3a). Pathway analysis using the KEGG database showed that the three most relevant pathways as interleukin (IL)-17 signaling, nuclear factor kappa B (NF-κB) signaling, and tumor necrosis factor (TNF) signaling (Table 2a). In the network of DEGs of V/E compared with those of V/S, *Egr1* (degree = 9, betweenness = 42.5) was located in the center, directly connecting 9 other genes (Fig. 3b). The three KEGG pathways most relevant to DEGs of M/S vs. V/S were mitophagy, NF-κB signaling, and advanced glycation end products (AGE)–receptor for advanced glycation end products (RAGE) signaling (Table 2b). Finally, in the network of DEGs of M/S compared to V/S, *S1pr1* (degree = 5, betweenness = 10) was in the center, directly connecting 5 other genes (Fig. 3c). The three KEGG pathways most relevant to DEGs of M/S vs. V/S were long-term depression, GABAergic synapse, and morphine addiction (Table 2c).

qPCR analyses

As described in the "Methods" section, the genes with a log2FC of > 1 or < − 1, and the genes coding the proteins with degree of ≥ 3 in the gene regulatory network, were included in the qPCR analyses. In total, 29 genes were targeted for qPCR analyses. The expression levels relative to actin and corresponding *P*-values are shown in Supplementary Table 4.

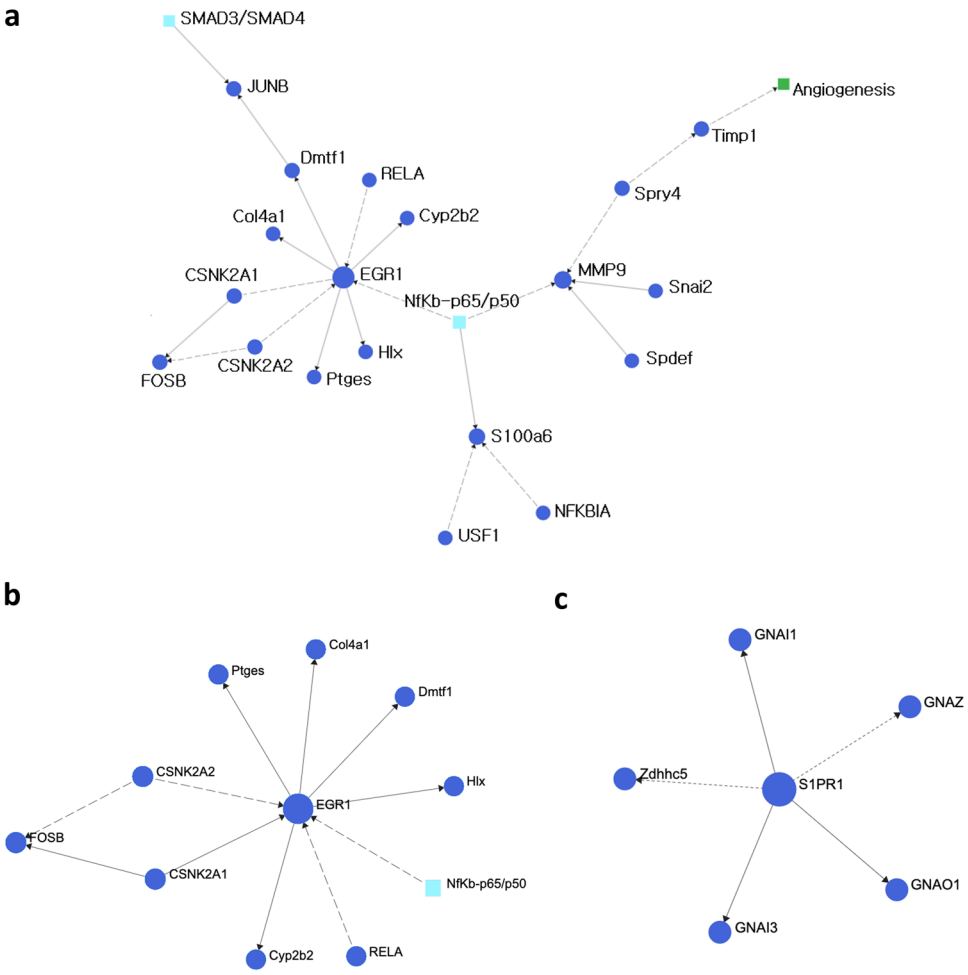

Fig. 3 Gene regulatory networks of DEGs. The figure illustrates gene regulatory networks of DEGs in **a** M/E versus M/S model, **b** V/E versus V/S model, and **c** M/S versus V/S model. Arrows show the direction from an upstream regulator to a downstream target. Shapes and colors are denoted as follows: circles = proteins, squares = complexes, blue = proteins, teal = complexes, and green = phenotypes. Abbreviations: V/S, vehicle-sham shock × 10 days (Sham) group; V/E, vehicle-ECS × 10 days (E10X) group; M/S, MK-801-Sham group; M/E, MK-801-E10X group

Table 2 Annotation results of the top three KEGG pathways enriched in the gene regulatory network

KEGG pathway	Hits	Expected	*P* value	FDR
(a) Network based on DEG between M/E and M/S				
IL-17 signaling pathway	4	0.141	8.72E-06	1.70E-03
NF-kappa B signaling pathway	4	0.152	1.16E-05	1.70E-03
TNF signaling pathway	4	0.165	1.62E-05	1.70E-03
(b) Network based on DEG between V/E and V/S				
Mitophagy	3	0.0596	2.15E-05	6.74E-03
NF-kappa B signaling pathway	3	0.0935	8.31E-05	8.95E-03
AGE-RAGE signaling pathway	3	0.0944	8.55E-05	8.95E-03
(c) Network based on DEG between M/S and V/S				
Long-term depression	4	0.0355	1.15E-08	3.60E-06
GABAergic synapse	3	0.0527	1.12E-05	8.20E-04
Morphine addiction	3	0.0533	1.15E-05	8.20E-04

(a) DEGs between M/E and M/S, (b) DEGs between V/E and V/S, and (c) DEGs between M/S and V/S. For each pathway, the pathway name, number of hits, expected number of genes, *P*-value, and FDR are listed. Abbreviations: *DEG*, differentially expressed genes; *IL-17*, interleukin-17; *NF*, nuclear factor; *TNF*, tumor necrosis factor; *AGE-RAGE*, advanced glycation end products-receptor for advanced glycation end products; *V/S*, vehicle-sham shock × 10 days (Sham) group; *V/E*, vehicle-ECS × 10 days group (E10X); *M/S*, MK-801-Sham group; *M/E*, MK-801-E10X group

Twenty genes were selected for qPCR analysis in the comparison of M/E and M/S (*Crabp1*, *Mmp9*, *Sprr1a*, *Igfbp6*, *Aqp1*, *Cd74*, *Lgals3*, *Ecel1*, *S100a6*, *Timp1*, *Dusp6*, *Egr1*, *Nr4a3*, *Junb*, *Egr4*, *Egr2*, *Ptgds*, *Fosb*, *Fos*, and *Harbi1*, from highest to lowest fold change). Eight upregulated genes (*Crabp1*, *Mmp9*, *Sprr1a*, *Igfbp6*, *Cd74*, *Lgals3*, *Ecel1*, and *S100a6*, from highest to lowest absolute fold change magnitude) and four downregulated genes (*Harbi1*, *Fos*, *Fosb*, and *Egr2*, from highest to lowest absolute fold change magnitude) showed significant differences in qPCR (Fig. 4a). Among the three central genes in the corresponding regulatory network, *Egr1* expression was significantly lower, and *S100a6* and *Mmp9* expression was significantly higher, in M/E than in M/S.

Twelve genes were selected for qPCR analysis in the comparison of V/E and V/S (*Crabp1*, *Calml4*, *Aqp1*, *Timp1*, *Egr1*, *Nr4a3*, *Ptgds*, *Egr4*, *Fosb*, *Pdyn*, *Fos*, and *Cox6a2*, from highest to lowest fold change). Four upregulated genes (*Crabp1*, *Calml4*, *Aqp1*, and *Timp1*, from highest to lowest absolute fold change magnitude) and four downregulated genes (*Fos*, *Pdyn*, *Fosb*, and *Egr4*, from highest to lowest absolute fold change magnitude) showed significant differences in qPCR (Fig. 4b). *Egr1*, the central gene in the corresponding regulatory network, had a significantly lower expression level in V/E than in V/S.

Seven genes were selected for qPCR analysis in the comparison of M/S and V/S (*Mx2*, *S1pr1*, *Lmo2*, *Btf3*, *H2az1*, *Pde4a*, and *Igfbp6*, from highest to lowest fold change). Although *Mx2*, an upregulated gene, did not show a significant difference, three downregulated genes (*Igfbp6*, *H2az1*, and *Btf3*, from highest to lowest absolute fold change magnitude) showed significant differences in qPCR (Fig. 4c). *S1pr1*, the central gene in the corresponding regulatory network, showed no significant difference.

Discussion

The present study examined the behavioral and transcriptomic effects of repeated ECS in an animal model of schizophrenia. Neonatal treatment of MK-801 induced PPI deficits in young adult rats, confirming the relevance of this treatment for establishing a neurodevelopmental animal model. Repeated ECS treatments normalized the MK-801-derived PPI deficits and induced significant alterations in the PFC transcriptome of MK-801-treated animals. Comparison of the transcriptomes between M/E and M/S, showing the effects of repeated ECS on neonatal MK-801-treated animals, revealed 53 DEGs. The network analysis of DEGs identified *Egr1*, *Mmp9*, and *S100a6* as central genes of the regulatory network, and KEGG pathway enrichment analyses showed that IL-17, NF-κB, and TNF signaling were the three most relevant pathways in this comparison. Among the downregulated genes in the MK-801-treated group, *Igfbp6*, *Btf3*, *Cox6a2*, and *H2az1* recovered their respective expression level with repeated ECS treatments. The findings demonstrate that repeated ECS treatments confer antipsychotic-like benefits in the animal models of psychosis and imply that such an effect likely involves gene networks that regulate immune, insulin, and mitophagy pathways.

Sensorimotor gating dysfunction is a central mechanism in the pathogenesis of schizophrenia (San-Martin et al. 2020; Swerdlow and Light 2018). Because PPI can be used to quantitatively measure sensorimotor gating function in both humans and animals (Garcia-Mompo et al. 2020; Miller et al. 2021; San-Martin et al. 2020; Tsivion-Visbord et al. 2020), PPI has been utilized as a standard behavioral measure in animal models of psychosis (Bialon and Wasik 2022; Khan and Powell 2018; Swerdlow and Light 2018). PPI deficits induced by perinatal antagonism of NMDA receptors have been demonstrated repeatedly (Li et al. 2016; Lim et al. 2012b; Phensy et al. 2017; Uehara et al. 2009) and were confirmed in the present study. ECS has been demonstrated to normalize PPI in rats selectively bred for high and low PPI (John et al. 2016), in rats with methamphetamine-induced psychotomimetic conditions (Chao et al. 2012), and in Gunn rats with schizophrenia-like behaviors (Limoa et al. 2016). This study also confirmed the antipsychotic effect of

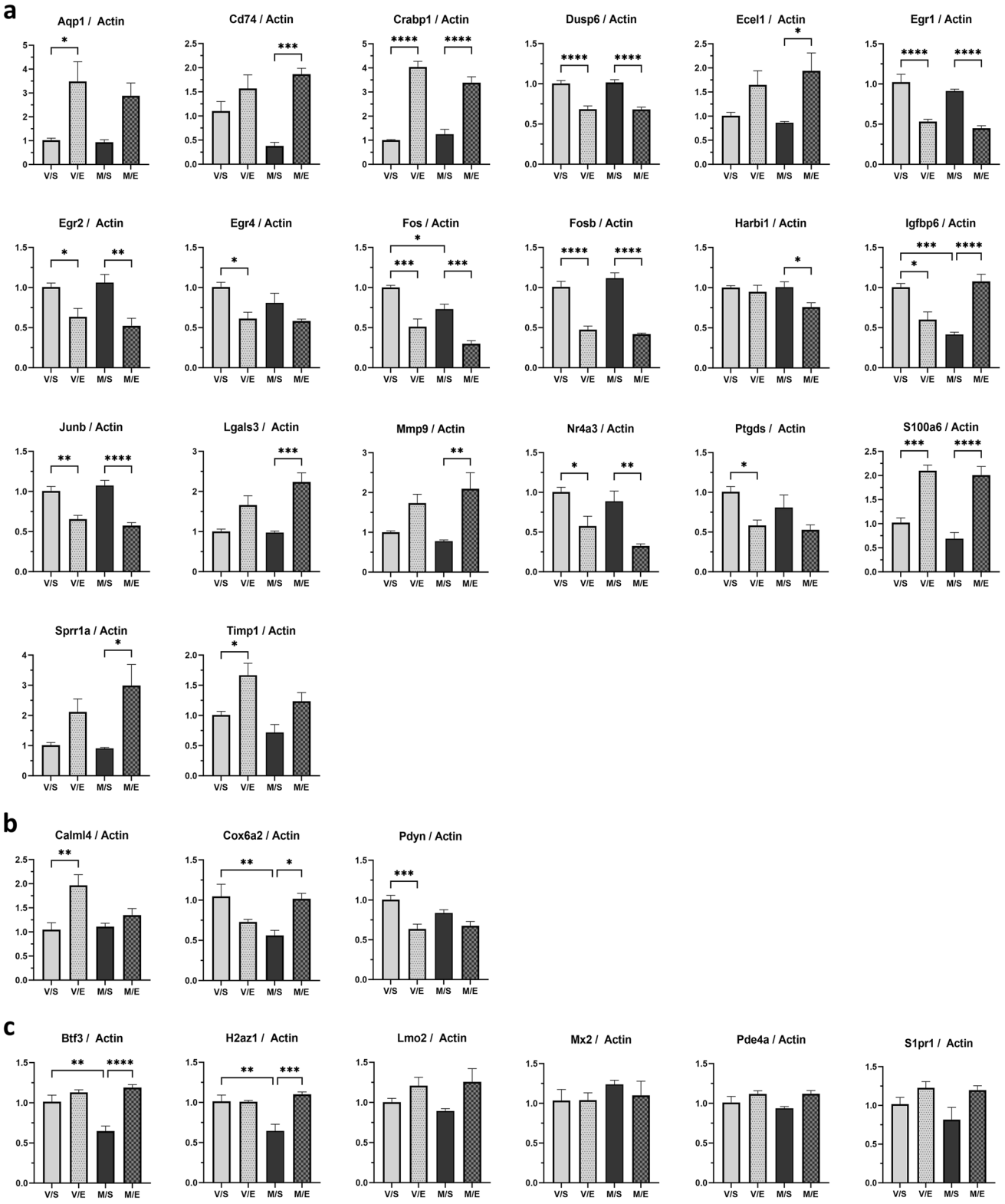

Fig. 4 Real-time qPCR analysis results. qPCR graphs of **a** genes included in DEGs between M/E and M/S, **b** genes included in DEGs between V/E and V/S, and **c** genes included in DEGs between M/S and V/S are shown. Genes already listed in **a** are not shown in **b** or **c**. The relative mRNA expression level of each gene was normalized to actin with the comparative Ct method, with the expression level of V/S set as 1.0. In each group, the graphs are organized in alphabetical order of gene names. $*P<0.05$, $**P<0.01$, $***P<0.001$, and $****P<0.0001$ (significant differences between groups). Abbreviations: V/S, vehicle-sham shock × 10 days (Sham) group; V/E, vehicle-ECS × 10 days (E10X) group; M/S, MK-801-Sham group; M/E, MK-801-E10X group

repeated ECS treatments, which normalized the sensorimotor deficits produced by the neonatal MK-801 treatment.

The long-term effects of MK-801 on spontaneous locomotor activity of rodents are mixed: the activity level increases, does not significantly change, or decreases depending on the experimental conditions (Akosman et al. 2021; Guneri et al. 2021; Kawabe and Miyamoto 2019; Lim et al. 2012a; b; Murueta-Goyena et al. 2018). In this study, neonatal MK-801 injection induced no significant effect on the locomotor activity level on PN59, and repeated ECS treatments led to a decreasing trend in the activity level. Systemic treatment of NMDA receptor antagonists induces dose-dependent changes in the locomotor activity level of rodents. In adult rodent models, a lower dose of MK-801 induces hyperactivity, while a higher dose induces either no changes or hypoactivity (Ahn et al. 2006; Gururajan et al. 2011; Kawabe and Miyamoto 2019; Liljequist et al. 1991). In the present study, MK-801 was injected twice daily at an 8-h interval using a dose of 1.0 mg/kg, which is higher than the doses of 0.1 mg/kg (Xiao et al. 2019), 0.2 mg/kg (Kraeuter et al. 2020), and 0.3 mg/kg (Cui et al. 2022) that produced hyperlocomotion in rodents. Although there is no clear relationship between the administered dose of the perinatal NMDA receptor antagonist and adult locomotor activity (Lim et al. 2012a), the MK-801 dose that affects the activity level in the adult period requires further clarification. Moreover, based on the two-hit hypothesis (Khan and Powell 2018; Lim et al. 2012b), additional stimuli during the adult period (after the early life manipulation) may induce more prominent psychotomimetic changes, such as hyperlocomotion, in rodent animal model (Lim et al. 2012b; Zhao et al. 2013). In this study, no additional stimulus was applied after the prenatal treatment, which may explain the lack of changes in locomotor activity. The repeated ECS treatments in this study reduced the activity level of rats, as reported in previous literature (Batterman et al. 2019; Park et al. 2011). Further investigation using a different MK-801 dose or an additional provocation will be needed to confirm the effects of repeated ECS on rodent hyperactivity.

Egr1, *NfKb-p65/p50*, *Mmp9*, and *S100a6* were identified as central genes in the network model of the effects of repeated ECSs in the psychosis animal model. *Egr* family genes, which are zinc finger transcriptional regulators involved in synaptic plasticity and memory, are implicated in schizophrenia (Cheng et al. 2012; Kim et al. 2010b; Yamada et al. 2007). Accordingly, a biological pathway that integrates NMDA receptors, *Egr* family genes, and long-term depression has been suggested as a possible explanation for the pathophysiology of schizophrenia (Marballi and Gallitano 2018). Especially, *Egr1* has been shown to be a key gene in schizophrenia in expression studies (Cattane et al. 2015; Li et al. 2022c; Pouget et al. 2016; Xu et al. 2016). In the central nervous system, *Egr1* exhibits unique roles in synaptic plasticity regulation (Duclot and Kabbaj 2017; Pouget et al. 2016), dopamine signaling during social interactions (Tallafuss et al. 2022), and memory formation (Gallo et al. 2018; Marballi and Gallitano 2018; Veyrac et al. 2014). Downregulation of immediate early genes (IEGs) including *Egr1* by repeated seizures has been demonstrated in several studies (Calais et al. 2013; Kalinina et al. 2022; Tsankova et al. 2004). We previously reported that repeated ECS treatments downregulated the expression of IEGs, such as *Egr1*, *Egr2*, and *c-Fos*, and inhibited the cocaine-induced increase of these genes in the rat frontal cortex (Park et al. 2011) and that this process was mediated by the histone deacetylase 2 (Park et al. 2014). IEGs including *Egr1* are important modulators of antipsychotic-induced neuroplasticity as well (de Bartolomeis et al. 2017; Verma et al. 2006). Considering that IEGs were enriched in the network analysis of DEGs between samples of schizophrenia patients before and after electroconvulsive therapy (Peng et al. 2021), focusing on IEGs such as *Egr1* holds promise for future research into the mechanisms underlying the antipsychotic effects of ECT.

In our pathway analysis, the IL-17, NF-κB, and TNF signaling pathways were identified as key enriched KEGG pathways in the regulatory network of repeated ECS treatments in psychosis animal models. NF-κB, a central pro-inflammatory transcription factor, induces several inflammatory cytokines, activates immune cells, and regulates inflammasomes; however, its dysregulation leads to inflammatory diseases and tumorigenesis (Liu et al. 2017; Yu et al. 2020). In the central nervous system, NF-κB plays important roles in synaptic plasticity and neurogenesis and protects neurons from injury; however, inducible NF-κB in glia causes neuronal damage that can lead to various neuroinflammation-associated pathogenesis (Shih et al. 2015). Neuroinflammation plays a critical role in schizophrenia, as numerous studies have reported an association between the two (Bae et al. 2023; Pandurangi and Buckley 2020; Rahman et al. 2022; Zhu et al. 2021). Patients with schizophrenia show elevated concentrations of plasma inflammatory markers, including NF-κB (de Bartolomeis et al. 2022; Kartalci et al. 2016; Miller and Goldsmith 2020; Muller et al. 2015), as well as upregulated NF-κB transcripts in the PFC (Murphy et al. 2021). Consequently, neuroinflammation is increasingly becoming the focus in terms of the pathogenesis of schizophrenia, as well as a therapeutic target (Messina et al. 2023; Miller and Goldsmith 2020; Mongan et al. 2020). NF-κB deserves particular attention because of cortical immune activation (Volk et al. 2019) and its involvement in the dysregulation of susceptible genes in schizophrenia (Long et al. 2022). Antipsychotics are known to reduce inflammation by attenuating cytokine expression (Dutheil et al. 2023; Patlola et al. 2023), including NF-κB (Al Abadey et al. 2022; Zhu et al. 2019). We have previously reported that the antipsychotic agent clozapine exerts

anti-inflammatory actions via the NF-κB signaling pathway (Jeon et al. 2018). Likewise, repeated ECT treatments attenuate inflammation in the long term (Gammon et al. 2021; Maffioletti et al. 2021; Yrondi et al. 2018). ECT reduces the concentrations of inflammatory cytokines (Xu et al. 2016; Yrondi et al. 2018) and NF-κB in patients with severe mental disorders, including schizophrenia (Bioque et al. 2019; Xu et al. 2016). Because the change in inflammatory biomarkers likely predicts the ECT response, the involvement of inflammation-related mechanisms in the therapeutic action of ECT has been suggested (Dogaru et al. 2022; Kruse et al. 2018). The findings from the previous studies and this study suggest that inflammatory signaling pathways can mediate the antipsychotic effects of ECT.

Other important genes identified as the central genes in this study are *Mmp9* and *S100a6*. Matrix metalloproteinase-9 (MMP-9) in the central nervous system regulates dendritic and synaptic dynamics (Li et al. 2022b), maintains NMDA-dependent long-term potentiation (Beroun et al. 2019), and regulates neuroinflammation by focally activating chemokines (Hannocks et al. 2019). MMP-9 is also implicated in the pathophysiology of schizophrenia (Beroun et al. 2019; Keshri and Nandeesha 2023; Lepeta and Kaczmarek 2015). Reduced activity of MMP-9 in the brain induces schizophrenia-like behaviors in mice (Vafadari et al. 2019). MMP-9 was also found to be elevated in patients with clozapine-treated schizophrenia (Yamamori et al. 2013). Consistent with previous literature, the present study showed that repeated ECS treatments upregulate MMP-9 (Girgenti et al. 2011). Therefore, the therapeutic action of repeated ECS treatments may involve the regulation of MMP-9.

S100A6, a member of the calcium-binding protein family, is involved in cellular repair and regeneration (Lesniak and Filipek 2023) and attenuates inflammatory responses via the PI3K/Akt pathway (Zhang et al. 2021). S100A6 is increased in status epilepticus (Jurewicz et al. 2013) and neurodegenerative disorders (Filipek and Lesniak 2020), whereas it is decreased under chronic stress (Bartkowska et al. 2017). Although the present study suggests that repeated ECS treatments upregulate S100 proteins (Huang and Chen 2008), future studies are needed to confirm this finding. In our pathway analysis, the AGE-RAGE signaling pathway was a key enriched pathway in repeated ECS treatments. This pathway, which is involved in impaired downstream insulin signaling (Khalid et al. 2022), can interact with S100 proteins and plays pivotal roles in immunity (Rouhiainen et al. 2013; Yatime et al. 2016).

This study illustrated the downregulation of *Igfbp6* induced by MK-801 and subsequent normalization by repeated ECS treatments. Schizophrenia is associated with abnormalities in insulin signaling (Agarwal et al. 2020a), and antipsychotics affect central insulin signaling, which may be related to therapeutic mechanism (Agarwal et al. 2020b; Kowalchuk et al. 2019). Insulin-like growth factor binding protein (IGFBP) family proteins modulate insulin growth factor receptor signaling (Baxter 2023); its member protein, IGFBP-6, regulates apoptosis and cell migration in the central nervous system (Bei et al. 2017; Dai et al. 2017). Schizophrenia is associated with decreased levels of IGFBP family proteins (Weissleder et al. 2021; Yang et al. 2020). Moreover, antipsychotic use upregulates circulating levels of an IGFBP (Fernandez-Pereira et al. 2022). The present study is the first to show that repeated ECS treatments rescue IGFBP-6 expression altered by a psychotomimetic condition, indicating that the therapeutic action of repeated ECS may involve IGFBP-6-induced modulation of insulin signaling.

Mitophagy, a selective degradation autophagy process of damaged mitochondria (Li et al. 2022a), was another key enriched pathway in the repeated ECS treatments of the present study. In the central nervous system, mitophagy plays key roles in synapse regulation and parvalbumin interneuron alterations (Khadimallah et al. 2022; Palikaras and Tavernarakis 2020). Mitophagy is linked to NF-κB through the p62-mitophagy pathway, which serves as a self-regulatory mechanism for NF-κB (Zhong et al. 2016). Schizophrenia is a neuropsychiatric disorder with disrupted mitophagy or autophagy processes (Merenlender-Wagner et al. 2015; Panda and Singh 2023; Yang and Xu 2020). Conversely, antipsychotics induce autophagy by stimulating related cellular pathways and may reduce neuronal dysfunction in schizophrenia (Kim et al. 2018b; Otreba et al. 2023; Vucicevic et al. 2018; Yang and Xu 2020; Zhu et al. 2019). We and others previously reported that repeated ECS treatments stimulated autophagy signaling and related pathways, such as the adenosine monophosphate-activated protein kinase pathway (Huh et al. 2023; Kim et al. 2022; Otabe et al. 2014). The present findings suggest the importance of mitophagy and autophagy in the therapeutic action of repeated ECS treatments and indicate the need for more studies to elucidate this relationship.

Other genes normalized by repeated ECS treatments in this animal model of psychosis include *Cox6a2*, *Btf3*, and *H2az1*; however, data on the relationship of these genes to schizophrenia are limited. The level of COX6A2 was reduced in an animal model of schizophrenia and displayed potential as a schizophrenia biomarker (Khadimallah et al. 2022). BTF3, along with other molecules, contributes to mitochondrial fusion and neuroprotection (Zeng et al. 2021). H2A.z supports normal neuronal differentiation and dendrite structure, and its absence causes behavioral abnormalities (Shen et al. 2018). Our results suggest that these proteins serve important roles in the antipsychotic action of repeated ECS treatments. Considering their above-described roles in the central nervous system, these proteins will be of particular interest for future studies.

In conclusion, this study illustrated the molecular mechanism underlying the antipsychotic-like action of repeated ECS treatments in an MK-801 schizophrenia animal model. In our experimental condition, the PPI deficit caused by neonatal MK-801 treatment was normalized with repeated ECS treatments, whereas locomotor activity remained unaffected. Thus, the transcriptomic alterations observed in this study may be associated with the changes in sensorimotor gating in psychosis model rodents, but their direct relationship requires further investigation. The sequencing analysis and subsequent pathway analysis revealed that the therapeutic mechanism of ECS likely involves the modulation of molecular pathways related to neuroinflammation, IEGs, insulin signaling, and mitophagy processes. Key genes in these analyses were confirmed by qPCR analysis. Additional studies, especially those investigating the therapeutic potential of the promising genes identified in this study, are needed to validate the present findings and shed light on clinical correlations.

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Declarations

Conflict of interest The authors declare no competing interests.

References

Abekawa T, Ito K, Nakagawa S, Koyama T (2007) 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 in postpubertal rats. Psychopharmacology 192:303–316

Agarwal SM, Caravaggio F, Costa-Dookhan KA, Castellani L, Kowalchuk C, Asgariroozbehani R, Graff-Guerrero A, Hahn M (2020a) Brain insulin action in schizophrenia: something borrowed and something new. Neuropharmacology 163:107633

Agarwal SM, Kowalchuk C, Castellani L, Costa-Dookhan KA, Caravaggio F, Asgariroozbehani R, Chintoh A, Graff-Guerrero A, Hahn M (2020b) Brain insulin action: implications for the treatment of schizophrenia. Neuropharmacology 168:107655

Ahn YM, Seo MS, Kim SH, Kim Y, Juhnn YS, Kim YS (2006) The effects of MK-801 on the phosphorylation of Ser338-c-Raf-MEK-ERK pathway in the rat frontal cortex. Int J Neuropsychopharmacol 9:451–456

Akosman MS, Turkmen R, Demirel HH (2021) Investigation of the protective effect of resveratrol in an MK-801-induced mouse model of schizophrenia. Environ Sci Pollut Res Int 28:65872–65884

Al Abadey A, Connor B, Flamme AC, Robichon K (2022) Clozapine reduces chemokine-mediated migration of lymphocytes by targeting NF-kappaB and AKT phosphorylation. Cell Signal 99:110449

Ali SA, Mathur N, Malhotra AK, Braga RJ (2019) Electroconvulsive therapy and schizophrenia: a systematic review. Mol Neuropsychiatry 5:75–83

Artigas F (2010) The prefrontal cortex: a target for antipsychotic drugs. Acta Psychiatr Scand 121:11–21

Bae HJ, Bae HJ, Kim JY, Park K, Yang X, Jung SY, Park SJ, Kim DH, Shin CY, Ryu JH (2023) The effect of lansoprazole on MK-801-induced schizophrenia-like behaviors in mice. Prog Neuropsychopharmacol Biol Psychiatry 120:110646

Bartkowska K, Swiatek I, Aniszewska A, Jurewicz E, Turlejski K, Filipek A, Djavadian RL (2017) Stress-dependent changes in the CacyBP/SIP interacting protein S100A6 in the mouse brain. PLoS One 12:e0169760

Batterman AI, DeChiara J, Islam A, Brenner MB, Fischer BD, Buono RJ, Keck TM, Ferraro TN (2019) Cognitive and behavioral effects of brief seizures in mice. Epilepsy Behav 98:249–257

Baxter RC (2023) Signaling pathways of the insulin-like growth factor binding proteins. Endocr Rev 44:753–778

Bei Y, Huang Q, Shen J, Shi J, Shen C, Xu P, Chang H, Xia X, Xu L, Ji B, Chen J (2017) IGFBP6 regulates cell apoptosis and migration in glioma. Cell Mol Neurobiol 37:889–898

Belforte JE, Zsiros V, Sklar ER, Jiang Z, Yu G, Li Y, Quinlan EM, Nakazawa K (2010) Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat Neurosci 13:76–83

Beroun A, Mitra S, Michaluk P, Pijet B, Stefaniuk M, Kaczmarek L (2019) MMPs in learning and memory and neuropsychiatric disorders. Cell Mol Life Sci 76:3207–3228

Bialon M, Wasik A (2022) Advantages and limitations of animal schizophrenia models. Int J Mol Sci 23:5968

Bioque M, Mac-Dowell KS, Meseguer A, Macau E, Valero R, Vieta E, Leza JC, Bernardo M (2019) Effects of electroconvulsive therapy in the systemic inflammatory balance of patients with severe mental disorder. Psychiatry Clin Neurosci 73:628–635

Bolon B, Dostal LA, Garman RH (2021) Neuropathology evaluation in juvenile toxicity studies in rodents: comparison of developmental neurotoxicity studies for chemicals with juvenile animal studies for pediatric pharmaceuticals. Toxicol Pathol 49:1405–1415

Bygrave AM, Kilonzo K, Kullmann DM, Bannerman DM, Katzel D (2019) Can N-methyl-D-aspartate receptor hypofunction in schizophrenia be localized to an individual cell type? Front Psychiatry 10:835

Calais JB, Valvassori SS, Resende WR, Feier G, Athie MC, Ribeiro S, Gattaz WF, Quevedo J, Ojopi EB (2013) Long-term decrease in immediate early gene expression after electroconvulsive seizures. J Neural Transm (Vienna) 120:259–266

Cattane N, Minelli A, Milanesi E, Maj C, Bignotti S, Bortolomasi M, Bocchio Chiavetto L, Gennarelli M (2015) Altered gene expression in schizophrenia: findings from transcriptional signatures in fibroblasts and blood. PLoS One 10:e0116686

Chang AD, Vaidya PV, Retzbach EP, Chung SJ, Kim U, Baselice K, Maynard K, Stepanian A, Staley M, Xiao L, Blouin A, Han S, Lee J, Worley PF, Tamashiro KL, Hempstead BL, Martinowich K, Ann Wilson M, Baraban JM, Reti IM (2018) Narp mediates antidepressant-like effects of electroconvulsive seizures. Neuropsychopharmacology 43:1088–1098

Chao YL, Chen HH, Chen CH (2012) Effects of repeated electroconvulsive shock on methamphetamine-induced behavioral abnormalities in mice. Brain Stimul 5:393–401

Cheng MC, Chuang YA, Lu CL, Chen YJ, Luu SU, Li JM, Hsu SH, Chen CH (2012) Genetic and functional analyses of early growth response (EGR) family genes in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 39:149–155

Cui K, Yu Z, Xu L, Jiang W, Wang L, Wang X, Zou D, Gu J, Gao F, Zhang X, Wang Z (2022) Behavioral features and disorganization

of oscillatory activity in C57BL/6J mice after acute low dose MK-801 administration. Front Neurosci 16:1001869
Dai Q, Jiang P, Gu Y, Zhu L, Dai H, Yao Z, Liu H, Ma X, Duan C, Qu L (2017) Insulin-like growth factor binding protein6 associated with neuronal apoptosis following intracerebral hemorrhage in rats. Cell Mol Neurobiol 37:1207–1216
de Bartolomeis A, Barone A, Vellucci L, Mazza B, Austin MC, Iasevoli F, Ciccarelli M (2022) Linking inflammation, aberrant glutamate-dopamine interaction, and post-synaptic changes: translational relevance for schizophrenia and antipsychotic treatment: a systematic review. Mol Neurobiol 59:6460–6501
de Bartolomeis A, Buonaguro EF, Latte G, Rossi R, Marmo F, Iasevoli F, Tomasetti C (2017) Immediate-early genes modulation by antipsychotics: translational implications for a putative gateway to drug-induced long-term brain changes. Front Behav Neurosci 11:240
de Mangoux GC, Amad A, Quilès C, Schürhoff F, Pignon B (2022) History of ECT in schizophrenia: from discovery to current use. Schizophrenia Bulletin Open 3:sgac053
Dogaru IA, Puiu MG, Manea M, Dionisie V (2022) Current perspectives on pharmacological and non-pharmacological interventions for the inflammatory mechanism of unipolar depression. Brain Sci 12:1403
Duclot F, Kabbaj M (2017) The role of early growth response 1 (EGR1) in brain plasticity and neuropsychiatric disorders. Front Behav Neurosci 11:35
Dutheil S, Watson LS, Davis RE, Snyder GL (2023) Lumateperone normalizes pathological levels of acute inflammation through important pathways known to be involved in mood regulation. J Neurosci 43:863–877
Enomoto S, Shimizu K, Nibuya M, Suzuki E, Nagata K, Kondo T (2017) Activated brain-derived neurotrophic factor/TrkB signaling in rat dorsal and ventral hippocampi following 10-day electroconvulsive seizure treatment. Neurosci Lett 660:45–50
Fernandez-Pereira C, Penedo MA, Rivera-Baltanas T, Fernandez-Martinez R, Ortolano S, Olivares JM, Agis-Balboa RC (2022) Insulin-like growth factor 2 (IGF-2) and insulin-like growth factor binding protein 7 (IGFBP-7) are upregulated after atypical antipsychotics in spanish schizophrenia patients. Int J Mol Sci 23:9591
Filipek A, Lesniak W (2020) S100A6 and its brain ligands in neurodegenerative disorders. Int J Mol Sci 21:3979
Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, Kulkarni J, McGorry P, Nielssen O, Tran N (2016) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 50:410–472
Galletly C, Clarke P, Paterson T, Rigby A, Gill S (2014) Practical considerations in the use of ultrabrief ECT in clinical practice. J ECT 30:10–14
Gallo FT, Katche C, Morici JF, Medina JH, Weisstaub NV (2018) Immediate early genes, memory and psychiatric disorders: focus on c-Fos, Egr1 and Arc. Front Behav Neurosci 12:79
Gammon D, Cheng C, Volkovinskaia A, Baker GB, Dursun SM (2021) Clozapine: why is it so uniquely effective in the treatment of a range of neuropsychiatric disorders? biomolecules 11:1030
Garcia-Mompo C, Curto Y, Carceller H, Gilabert-Juan J, Rodriguez-Flores E, Guirado R, Nacher J (2020) Delta-9-Tetrahydrocannabinol treatment during adolescence and alterations in the inhibitory networks of the adult prefrontal cortex in mice subjected to perinatal NMDA receptor antagonist injection and to postweaning social isolation. Transl Psychiatry 10:177
Gentleman RC, Carey VJ, Bates DM, Bolstad B, Dettling M, Dudoit S, Ellis B, Gautier L, Ge Y, Gentry J, Hornik K, Hothorn T, Huber W, Iacus S, Irizarry R, Leisch F, Li C, Maechler M, Rossini AJ, Sawitzki G, Smith C, Smyth G, Tierney L, Yang JY, Zhang J (2004) Bioconductor: open software development for computational biology and bioinformatics. Genome Biol 5:R80
Girgenti MJ, Collier E, Sathyanesan M, Su XW, Newton SS (2011) Characterization of electroconvulsive seizure-induced TIMP-1 and MMP-9 in hippocampal vasculature. Int J Neuropsychopharmacol 14:535–544
Grover S, Chakrabarti S, Kulhara P, Avasthi A (2017) Clinical practice guidelines for management of schizophrenia. Indian J Psychiatry 59:S19–S33
Grover S, Sahoo S, Rabha A, Koirala R (2019) ECT in schizophrenia: a review of the evidence. Acta Neuropsychiatr 31:115–127
Guneri S, Scheel-Kruger J, Luo F (2021) Evaluation of acute and chronic nociception in subchronically administered MK-801-induced rat model of schizophrenia. Behav Pharmacol 32:571–580
Gururajan A, Taylor DA, Malone DT (2011) Effect of cannabidiol in a MK-801-rodent model of aspects of schizophrenia. Behav Brain Res 222:299–308
Hannocks MJ, Zhang X, Gerwien H, Chashchina A, Burmeister M, Korpos E, Song J, Sorokin L (2019) The gelatinases, MMP-2 and MMP-9, as fine tuners of neuroinflammatory processes. Matrix Biol 75–76:102–113
Hlavacova N, Hrivikova K, Karailievova L, Karailiev P, Homberg JR, Jezova D (2023) Altered responsiveness to glutamatergic modulation by MK-801 and to repeated stress of immune challenge in female dopamine transporter knockout rats. Prog Neuropsychopharmacol Biol Psychiatry 126:110804
Huang CT, Chen CH (2008) Identification of gene transcripts in rat frontal cortex that are regulated by repeated electroconvulsive seizure treatment. Neuropsychobiology 58:171–177
Huh S, Yu HS, Kang N, Ahn YM, Kim YS, Kim SH (2023) Electroconvulsive seizure normalizes motor deficits and induces autophagy signaling in the MPTP-induced Parkinson disease mouse model. Psychiatry Investig 20:273–283
Jeon S, Kim SH, Shin SY, Lee YH (2018) Clozapine reduces Toll-like receptor 4/NF-kappaB-mediated inflammatory responses through inhibition of calcium/calmodulin-dependent Akt activation in microglia. Prog Neuropsychopharmacol Biol Psychiatry 81:477–487
John N, Theilmann W, Frieling H, Krauss JK, Alam M, Schwabe K, Brandt C (2016) Cortical electroconvulsive stimulation alleviates breeding-induced prepulse inhibition deficit in rats. Exp Neurol 275(Pt 1):99–103
Jurewicz E, Bednarczyk J, Bot A, Lukasiuk K, Filipek A (2013) Status epilepticus induces long lasting increase in S100A6 expression in astrocytes. Neurochem Res 38:1941–1948
Kalinina A, Krekhno Z, Yee J, Lehmann H, Fournier NM (2022) Effect of repeated seizures on spatial exploration and immediate early gene expression in the hippocampus and dentate gyrus. IBRO Neurosci Rep 12:73–80
Kantrowitz JT, Javitt DC (2010) N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? Brain Res Bull 83:108–121
Kartalci S, Karabulut AB, Erbay LG, Acar C (2016) Effects of electroconvulsive therapy on some inflammatory factors in patients with treatment-resistant schizophrenia. J ECT 32:174–179
Kawabe K, Miyamoto E (2019) Effects of early postnatal MK-801 treatment on behavioral properties in rats: differences according to treatment schedule. Behav Brain Res 370:111926
Keshri N, Nandeesha H (2023) Dysregulation of synaptic plasticity markers in schizophrenia. Indian J Clin Biochem 38:4–12
Khadimallah I, Jenni R, Cabungcal JH, Cleusix M, Fournier M, Beard E, Klauser P, Knebel JF, Murray MM, Retsa C, Siciliano M, Spencer KM, Steullet P, Cuenod M, Conus P, Do KQ (2022) Mitochondrial, exosomal miR137-COX6A2 and gamma synchrony as biomarkers of parvalbumin interneurons,

psychopathology, and neurocognition in schizophrenia. Mol Psychiatry 27:1192–1204
Khalid M, Petroianu G, Adem A (2022) Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. Biomolecules 12:542
Khan A, Powell SB (2018) Sensorimotor gating deficits in "two-hit" models of schizophrenia risk factors. Schizophr Res 198:68–83
Kim JH, Youn T, Choi JG, Jeong SH, Jung HY, Kim YS, Chung IW (2018a) Combination of electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. Psychiatry Investig 15:829–835
Kim SH, Park HG, Kim HS, Ahn YM, Kim YS (2010a) Effects of neonatal MK-801 treatment on p70S6K-S6/eIF4B signal pathways and protein translation in the frontal cortex of the developing rat brain. Int J Neuropsychopharmacol 13:1233–1246
Kim SH, Park S, Yu HS, Ko KH, Park HG, Kim YS (2018b) The antipsychotic agent clozapine induces autophagy via the AMPK-ULK1-Beclin1 signaling pathway in the rat frontal cortex. Prog Neuropsychopharmacol Biol Psychiatry 81:96–104
Kim SH, Song JY, Joo EJ, Lee KY, Ahn YM, Kim YS (2010b) EGR3 as a potential susceptibility gene for schizophrenia in Korea. Am J Med Genet B Neuropsychiatr Genet 153B:1355–1360
Kim SH, Yu HS, Huh S, Kang UG, Kim YS (2022) Electroconvulsive seizure inhibits the mTOR signaling pathway via AMPK in the rat frontal cortex. Psychopharmacology 239:443–454
Kim SH, Yu HS, Park HG, Ha K, Kim YS, Shin SY, Ahn YM (2013) Intracerebroventricular administration of ouabain, a Na/K-ATPase inhibitor, activates mTOR signal pathways and protein translation in the rat frontal cortex. Prog Neuropsychopharmacol Biol Psychiatry 45:73–82
Kim SH, Yu HS, Park HG, Jeon WJ, Song JY, Kang UG, Ahn YM, Lee YH, Kim YS (2008) Dose-dependent effect of intracerebroventricular injection of ouabain on the phosphorylation of the MEK1/2-ERK1/2-p90RSK pathway in the rat brain related to locomotor activity. Prog Neuropsychopharmacol Biol Psychiatry 32:1637–1642
Kimura M, Oda Y, Oishi K, Yoshino K, Kimura H, Niitsu T, Kanahara N, Shirayama Y, Hashimoto K, Iyo M (2021) Effects of repeated electroconvulsive shocks on dopamine supersensitivity psychosis model rats. Schizophr Res 228:1–6
Kobayashi Y, Segi-Nishida E (2019) Search for factors contributing to resistance to the electroconvulsive seizure treatment model using adrenocorticotrophic hormone-treated mice. Pharmacol Biochem Behav 186:172767
Kowalchuk C, Kanagasundaram P, Belsham DD, Hahn MK (2019) Antipsychotics differentially regulate insulin, energy sensing, and inflammation pathways in hypothalamic rat neurons. Psychoneuroendocrinology 104:42–48
Kraeuter AK, Mashavave T, Suvarna A, van den Buuse M, Sarnyai Z (2020) Effects of beta-hydroxybutyrate administration on MK-801-induced schizophrenia-like behaviour in mice. Psychopharmacology 237:1397–1405
Kruse JL, Congdon E, Olmstead R, Njau S, Breen EC, Narr KL, Espinoza R, Irwin MR (2018) Inflammation and improvement of depression following electroconvulsive therapy in treatment-resistant depression. J Clin Psychiatry 79:17m11597
Langmead B, Salzberg SL (2012) Fast gapped-read alignment with Bowtie 2. Nat Methods 9:357–359
Lee JS, Yun JY, Kang SH, Lee SJ, Choi JH, Nam B, Lee SH, Chung YC, Kim CH (2020) Korean medication algorithm for schizophrenia 2019, second revision: treatment of psychotic symptoms. Clin Psychopharmacol Neurosci 18:386–394
Lepeta K, Kaczmarek L (2015) Matrix metalloproteinase-9 as a novel player in synaptic plasticity and schizophrenia. Schizophr Bull 41:1003–1009
Lesniak W, Filipek A (2023) S100A6 protein-expression and function in norm and pathology. Int J Mol Sci 24:1341
Li A, Gao M, Liu B, Qin Y, Chen L, Liu H, Wu H, Gong G (2022a) Mitochondrial autophagy: molecular mechanisms and implications for cardiovascular disease. Cell Death Dis 13:444
Li C, Tang Y, Yang J, Zhang X, Liu Y, Tang A (2016) Sub-chronic antipsychotic drug administration reverses the expression of neuregulin 1 and ErbB4 in a cultured MK801-induced mouse primary hippocampal neuron or a neurodevelopmental schizophrenia model. Neurochem Res 41:2049–2064
Li G, Xu S, Kang UG (2023) Characteristics of MK-801-induced locomotor sensitization. Biochem Biophys Res Commun 667:18–24
Li H, Sheng Z, Khan S, Zhang R, Liu Y, Zhang Y, Yong VW, Xue M (2022b) Matrix metalloproteinase-9 as an important contributor to the pathophysiology of depression. Front Neurol 13:861843
Li Z, Li X, Jin M, Liu Y, He Y, Jia N, Cui X, Liu Y, Hu G, Yu Q (2022c) Identification of potential biomarkers and their correlation with immune infiltration cells in schizophrenia using combinative bioinformatics strategy. Psychiatry Res 314:114658
Liljequist S, Ossowska K, Grabowska-Anden M, Anden NE (1991) Effect of the NMDA receptor antagonist, MK-801, on locomotor activity and on the metabolism of dopamine in various brain areas of mice. Eur J Pharmacol 195:55–61
Lim AL, Taylor DA, Malone DT (2012a) Consequences of early life MK-801 administration: long-term behavioural effects and relevance to schizophrenia research. Behav Brain Res 227:276–286
Lim AL, Taylor DA, Malone DT (2012b) A two-hit model: behavioural investigation of the effect of combined neonatal MK-801 administration and isolation rearing in the rat. J Psychopharmacol 26:1252–1264
Limoa E, Hashioka S, Miyaoka T, Tsuchie K, Arauchi R, Azis IA, Wake R, Hayashida M, Araki T, Furuya M, Liaury K, Tanra AJ, Horiguchi J (2016) Electroconvulsive shock attenuated microgliosis and astrogliosis in the hippocampus and ameliorated schizophrenia-like behavior of Gunn rat. J Neuroinflammation 13:230
Lisanby SH (2007) Electroconvulsive therapy for depression. N Engl J Med 357:1939–1945
Liu T, Zhang L, Joo D, Sun SC (2017) NF-kappaB signaling in inflammation. Signal Transduct Target Ther 2:17023-
Long J, Tian L, Baranova A, Cao H, Yao Y, Rao S, Zhang F (2022) Convergent lines of evidence supporting involvement of NFKB1 in schizophrenia. Psychiatry Res 312:114588
MacDonald ML, Eaton ME, Dudman JT, Konradi C (2005) Antipsychotic drugs elevate mRNA levels of presynaptic proteins in the frontal cortex of the rat. Biol Psychiatry 57:1041–1051
Maffioletti E, Carvalho Silva R, Bortolomasi M, Baune BT, Gennarelli M, Minelli A (2021) Molecular biomarkers of electroconvulsive therapy effects and clinical response: understanding the present to shape the future. brain sci 11:1120
Marballi KK, Gallitano AL (2018) Immediate early genes anchor a biological pathway of proteins required for memory formation, long-term depression and risk for schizophrenia. Front Behav Neurosci 12:23
Merenlender-Wagner A, Malishkevich A, Shemer Z, Udawela M, Gibbons A, Scarr E, Dean B, Levine J, Agam G, Gozes I (2015) Autophagy has a key role in the pathophysiology of schizophrenia. Mol Psychiatry 20:126–132
Messina A, Concerto C, Rodolico A, Petralia A, Caraci F, Signorelli MS (2023) Is it time for a paradigm shift in the treatment of schizophrenia? The use of inflammation-reducing and neuroprotective drugs-a review. Brain Sci 13:957
Meyers KT, Damphousse CC, Ozols AB, Campbell JM, Newbern JM, Hu C, Marrone DF, Gallitano AL (2023) Serial electroconvulsive seizure alters dendritic complexity and promotes cellular

proliferation in the mouse dentate gyrus; a role for Egr3. Brain Stimul 16:889–900
Miller BJ, Goldsmith DR (2020) Evaluating the hypothesis that schizophrenia is an inflammatory disorder. Focus (Am Psychiatr Publ) 18:391–401
Miller EA, Kastner DB, Grzybowski MN, Dwinell MR, Geurts AM, Frank LM (2021) Robust and replicable measurement for prepulse inhibition of the acoustic startle response. Mol Psychiatry 26:1909–1927
Minelli A, Abate M, Zampieri E, Gainelli G, Trabucchi L, Segala M, Sartori R, Gennarelli M, Conca A, Bortolomasi M (2016) Seizure adequacy markers and the prediction of electroconvulsive therapy response. J ECT 32:88–92
Mohammadi S, Asadi-Shekaari M, Basiri M, Parvan M, Shabani M, Nozari M (2020) Improvement of autistic-like behaviors in adult rats prenatally exposed to valproic acid through early suppression of NMDA receptor function. Psychopharmacology 237:199–208
Mongan D, Ramesar M, Focking M, Cannon M, Cotter D (2020) Role of inflammation in the pathogenesis of schizophrenia: a review of the evidence, proposed mechanisms and implications for treatment. Early Interv Psychiatry 14:385–397
Muller N, Weidinger E, Leitner B, Schwarz MJ (2015) The role of inflammation in schizophrenia. Front Neurosci 9:372
Murphy CE, Walker AK, Weickert CS (2021) Neuroinflammation in schizophrenia: the role of nuclear factor kappa B. Transl Psychiatry 11:528
Murueta-Goyena A, Ortuzar N, Gargiulo PA, Lafuente JV, Bengoetxea H (2018) Short-term exposure to enriched environment in adult rats restores MK-801-induced cognitive deficits and GABAergic interneuron immunoreactivity loss. Mol Neurobiol 55:26–41
Nakazawa K, Jeevakumar V, Nakao K (2017) Spatial and temporal boundaries of NMDA receptor hypofunction leading to schizophrenia. NPJ Schizophr 3:7
Nakazawa K, Sapkota K (2020) The origin of NMDA receptor hypofunction in schizophrenia. Pharmacol Ther 205:107426
Niu J, Cao Y, Ji Y (2020) Resveratrol, a SIRT1 activator, ameliorates MK-801-induced cognitive and motor impairments in a neonatal rat model of schizophrenia. Front Psychiatry 11:716
Otabe H, Nibuya M, Shimazaki K, Toda H, Suzuki G, Nomura S, Shimizu K (2014) Electroconvulsive seizures enhance autophagy signaling in rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry 50:37–43
Otreba M, Stojko J, Rzepecka-Stojko A (2023) The role of phenothiazine derivatives in autophagy regulation: a systematic review. J Appl Toxicol 43:474–489
Palikaras K, Tavernarakis N (2020) Regulation and roles of mitophagy at synapses. Mech Ageing Dev 187:111216
Panda SP, Singh V (2023) The dysregulated MAD in mad: a neurotheranostic approach through the induction of autophagic biomarkers LC3B-II and ATG. Mol Neurobiol 60:5214–5236
Pandurangi AK, Buckley PF (2020) Inflammation, antipsychotic drugs, and evidence for effectiveness of anti-inflammatory agents in schizophrenia. Curr Top Behav Neurosci 44:227–244
Park HG, Kim SH, Kim HS, Ahn YM, Kang UG, Kim YS (2011) Repeated electroconvulsive seizure treatment in rats reduces inducibility of early growth response genes and hyperactivity in response to cocaine administration. Prog Neuropsychopharmacol Biol Psychiatry 35:1014–1021
Park HG, Yu HS, Park S, Ahn YM, Kim YS, Kim SH (2014) Repeated treatment with electroconvulsive seizures induces HDAC2 expression and down-regulation of NMDA receptor-related genes through histone deacetylation in the rat frontal cortex. Int J Neuropsychopharmacol 17:1487–1500
Patlola SR, Donohoe G, McKernan DP (2023) Anti-inflammatory effects of 2nd generation antipsychotics in patients with schizophrenia: a systematic review and meta-analysis. J Psychiatr Res 160:126–136
Peng W, Tan Q, Yu M, Wang P, Wang T, Yuan J, Liu D, Chen D, Huang C, Tan Y, Liu K, Xiang B, Liang X (2021) Transcriptome sequencing reveals the potential mechanisms of modified electroconvulsive therapy in schizophrenia. Psychiatry Investig 18:385–391
Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, Kane JM, Sanghani S, Goldberg TE, John M, Mendelowitz A (2015) Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry 172:52–58
Phensy A, Duzdabanian HE, Brewer S, Panjabi A, Driskill C, Berz A, Peng G, Kroener S (2017) Antioxidant treatment with N-acetyl cysteine prevents the development of cognitive and social behavioral deficits that result from perinatal ketamine treatment. Front Behav Neurosci 11:106
Pouget JG, Goncalves VF, Schizophrenia Working Group of the Psychiatric Genomics C, Spain SL, Finucane HK, Raychaudhuri S, Kennedy JL, Knight J (2016) Genome-wide association studies suggest limited immune gene enrichment in schizophrenia compared to 5 autoimmune diseases. Schizophr Bull 42:1176–84
Quinlan AR, Clark RA, Sokolova S, Leibowitz ML, Zhang Y, Hurles ME, Mell JC, Hall IM (2010) Genome-wide mapping and assembly of structural variant breakpoints in the mouse genome. Genome Res 20:623–635
Rahman T, Purves-Tyson T, Geddes AE, Huang XF, Newell KA, Weickert CS (2022) N-Methyl-d-Aspartate receptor and inflammation in dorsolateral prefrontal cortex in schizophrenia. Schizophr Res 240:61–70
R Development Core Team (2016) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
Ritter LM, Vazquez DM, Meador-Woodruff JH (2002) Ontogeny of ionotropic glutamate receptor subunit expression in the rat hippocampus. Brain Res Dev Brain Res 139:227–236
Rouhiainen A, Kuja-Panula J, Tumova S, Rauvala H (2013) RAGE-mediated cell signaling. Methods Mol Biol 963:239–263
San-Martin R, Castro LA, Menezes PR, Fraga FJ, Simoes PW, Salum C (2020) Meta-analysis of sensorimotor gating deficits in patients with schizophrenia evaluated by prepulse inhibition test. Schizophr Bull 46:1482–1497
Sanghani SN, Petrides G, Kellner CH (2018) Electroconvulsive therapy (ECT) in schizophrenia: a review of recent literature. Curr Opin Psychiatry 31:213–222
Segi-Nishida E (2011) Exploration of new molecular mechanisms for antidepressant actions of electroconvulsive seizure. Biol Pharm Bull 34:939–944
Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ (2013) Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol 106–107:1–16
Shen T, Ji F, Wang Y, Lei X, Zhang D, Jiao J (2018) Brain-specific deletion of histone variant H2A.z results in cortical neurogenesis defects and neurodevelopmental disorder. Nucleic Acids Res 46:2290–2307
Shih RH, Wang CY, Yang CM (2015) NF-kappaB signaling pathways in neurological inflammation: a mini review. Front Mol Neurosci 8:77
Sinclair DJ, Zhao S, Qi F, Nyakyoma K, Kwong JS, Adams CE (2019) Electroconvulsive therapy for treatment-resistant schizophrenia. Cochrane Database Syst Rev 3:CD011847
Swerdlow NR, Light GA (2018) Sensorimotor gating deficits in schizophrenia: advancing our understanding of the phenotype, its neural circuitry and genetic substrates. Schizophr Res 198:1–5

Tallafuss A, Stednitz SJ, Voeun M, Levichev A, Larsch J, Eisen J, Washbourne P (2022) Egr1 is necessary for forebrain dopaminergic signaling during social behavior. eNeuro 9. https://doi.org/10.1523/ENEURO.0035-22.2022

Tartt AN, Mariani M, Hen R, Mann JJ, Boldrini M (2023) Electroconvulsive therapy-a shocking inducer of neuroplasticity? Mol Psychiatry. https://doi.org/10.1038/s41380-023-02015-0

Tricklebank MD, Singh L, Oles RJ, Preston C, Iversen SD (1989) The behavioural effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. Eur J Pharmacol 167:127–135

Tsankova NM, Kumar A, Nestler EJ (2004) Histone modifications at gene promoter regions in rat hippocampus after acute and chronic electroconvulsive seizures. J Neurosci 24:5603–5610

Tsivion-Visbord H, Perets N, Sofer T, Bikovski L, Goldshmit Y, Ruban A, Offen D (2020) Mesenchymal stem cells derived extracellular vesicles improve behavioral and biochemical deficits in a phencyclidine model of schizophrenia. Transl Psychiatry 10:305

Uehara T, Sumiyoshi T, Seo T, Itoh H, Matsuoka T, Suzuki M, Kurachi M (2009) Long-term effects of neonatal MK-801 treatment on prepulse inhibition in young adult rats. Psychopharmacology 206:623–630

Uttl L, Petrasek T, Sengul H, Svojanovska M, Lobellova V, Vales K, Radostova D, Tsenov G, Kubova H, Mikulecka A, Svoboda J, Stuchlik A (2018) Chronic MK-801 application in adolescence and early adulthood: a spatial working memory deficit in adult long-evans rats but no changes in the hippocampal NMDA receptor subunits. Front Pharmacol 9:42

Vafadari B, Mitra S, Stefaniuk M, Kaczmarek L (2019) Psychosocial stress induces schizophrenia-like behavior in mice with reduced MMP-9 activity. Front Behav Neurosci 13:195

Verma V, Rasmussen K, Dawe GS (2006) Effects of short-term and chronic olanzapine treatment on immediate early gene protein and tyrosine hydroxylase immunoreactivity in the rat locus coeruleus and medial prefrontal cortex. Neuroscience 143:573–585

Veyrac A, Besnard A, Caboche J, Davis S, Laroche S (2014) The transcription factor Zif268/Egr1, brain plasticity, and memory. Prog Mol Biol Transl Sci 122:89–129

Volk DW, Moroco AE, Roman KM, Edelson JR, Lewis DA (2019) The role of the nuclear factor-kappaB transcriptional complex in cortical immune activation in schizophrenia. Biol Psychiatry 85:25–34

Vucicevic L, Misirkic-Marjanovic M, Harhaji-Trajkovic L, Maric N, Trajkovic V (2018) Mechanisms and therapeutic significance of autophagy modulation by antipsychotic drugs. Cell Stress 2:282–291

Ward HB, Szabo ST, Rakesh G (2018) Maintenance ECT in schizophrenia: a systematic review. Psychiatry Res 264:131–142

Weiner RD, Reti IM (2017) Key updates in the clinical application of electroconvulsive therapy. Int Rev Psychiatry 29:54–62

Weissleder C, Webster MJ, Barry G, Shannon Weickert C (2021) Reduced insulin-like growth factor family member expression predicts neurogenesis marker expression in the subependymal zone in schizophrenia and bipolar disorder. Schizophr Bull 47:1168–1178

Xiao X, Xu X, Li F, Xie G, Zhang T (2019) Anti-inflammatory treatment with beta-asarone improves impairments in social interaction and cognition in MK-801 treated mice. Brain Res Bull 150:150–159

Xu Y, Yue W, Yao Shugart Y, Li S, Cai L, Li Q, Cheng Z, Wang G, Zhou Z, Jin C, Yuan J, Tian L, Wang J, Zhang K, Zhang K, Liu S, Song Y, Zhang F (2016) Exploring transcription factors-microRNAs co-regulation networks in schizophrenia. Schizophr Bull 42:1037–1045

Yamada K, Gerber DJ, Iwayama Y, Ohnishi T, Ohba H, Toyota T, Aruga J, Minabe Y, Tonegawa S, Yoshikawa T (2007) Genetic analysis of the calcineurin pathway identifies members of the EGR gene family, specifically EGR3, as potential susceptibility candidates in schizophrenia. Proc Natl Acad Sci U S A 104: 2815-20

Yamamori H, Hashimoto R, Ishima T, Kishi F, Yasuda Y, Ohi K, Fujimoto M, Umeda-Yano S, Ito A, Hashimoto K, Takeda M (2013) Plasma levels of mature brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in treatment-resistant schizophrenia treated with clozapine. Neurosci Lett 556:37–41

Yang Y, Xu L (2020) Autophagy and Schizophrenia. Adv Exp Med Biol 1207:195–209

Yang YJ, Luo T, Zhao Y, Jiang SZ, Xiong JW, Zhan JQ, Yu B, Yan K, Wei B (2020) Altered insulin-like growth factor-2 signaling is associated with psychopathology and cognitive deficits in patients with schizophrenia. PLoS One 15:e0226688

Yatime L, Betzer C, Jensen RK, Mortensen S, Jensen PH, Andersen GR (2016) The structure of the RAGE:S100A6 complex reveals a unique mode of homodimerization for S100 proteins. Structure 24:2043–2052

Youn T, Jeong SH, Kim YS, Chung IW (2019) Long-term clinical efficacy of maintenance electroconvulsive therapy in patients with treatment-resistant schizophrenia on clozapine. Psychiatry Res 273:759–766

Yrondi A, Sporer M, Peran P, Schmitt L, Arbus C, Sauvaget A (2018) Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. Brain Stimul 11:29–51

Yu H, Lin L, Zhang Z, Zhang H, Hu H (2020) Targeting NF-kappaB pathway for the therapy of diseases: mechanism and clinical study. Signal Transduct Target Ther 5:209

Zeng KW, Wang JK, Wang LC, Guo Q, Liu TT, Wang FJ, Feng N, Zhang XW, Liao LX, Zhao MM, Liu D, Jiang Y, Tu P (2021) Small molecule induces mitochondrial fusion for neuroprotection via targeting CK2 without affecting its conventional kinase activity. Signal Transduct Target Ther 6:71

Zhang XF, Ma JX, Wang YL, Ma XL (2021) Calcyclin (S100A6) attenuates inflammatory response and mediates apoptosis of chondrocytes in osteoarthritis via the PI3K/AKT pathway. Orthop Surg 13:1094–1101

Zhao YY, Li JT, Wang XD, Li YH, Huang RH, Su YA, Si TM (2013) Neonatal MK-801 treatment differentially alters the effect of adolescent or adult MK-801 challenge on locomotion and PPI in male and female rats. J Psychopharmacol 27:845–853

Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, He F, Boassa D, Perkins G, Ali SR, McGeough MD, Ellisman MH, Seki E, Gustafsson AB, Hoffman HM, Diaz-Meco MT, Moscat J, Karin M (2016) NF-kappaB restricts inflammasome activation via elimination of damaged mitochondria. Cell 164:896–910

Zhou G, Soufan O, Ewald J, Hancock REW, Basu N, Xia J (2019) NetworkAnalyst 3.0: a visual analytics platform for comprehensive gene expression profiling and meta-analysis. Nucleic Acids Res 47:W234–W241

Zhu H, Yang Y, Zhu M, Shi X, Ye L, Zhang S, Fang H, Yu W (2021) Alteration in the expression of inflammatory cytokines in primary hippocampal astrocytes in response to MK-801 through ERK1/2 and PI3K signals. Cytokine 138:155366

Zhu Y, Zhao YF, Liu RS, Xiong YJ, Shen X, Wang Y, Liang ZQ (2019) Olanzapine induced autophagy through suppression of NF-kappaB activation in human glioma cells. CNS Neurosci Ther 25:911–921