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Single Intraperitoneal Injection of Dexamethasone Alters Stress-Related Behavior and Endogenous Glucocorticoid Signaling in Rats

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Abstract

Introduction: Dexamethasone induces region-specific alterations in brain monoamine metabolism, but their functional significance and relationship to glucocorticoid regulation remain unclear.

Aim: This study evaluated the effects of a single dexamethasone administration at 8 mg/kg on rat behavior and glucocorticoid signaling in the hippocampus, striatum, and prefrontal cortex.

Method: Spatial learning and memory were assessed using the Morris water maze, stress-coping behavior using the forced swim test, and locomotor and exploratory activity using the open field test. Messenger ribonucleic acid levels of the glucocorticoid receptor, Jun proto-oncogene, and Fos proto-oncogene were measured, endogenous corticosterone was determined, and potential glucocorticoid response elements were analyzed *in silico*.

Results: Dexamethasone did not impair spatial learning, memory, or general locomotor activity but increased immobility and freezing and reduced active swimming and grooming. Glucocorticoid receptor messenger ribonucleic acid remained unchanged in all brain regions. Corticosterone decreased in the striatum and prefrontal cortex but not in the hippocampus. Jun proto-oncogene and Fos proto-oncogene messenger ribonucleic acid levels increased in the hippocampus, decreased in the striatum, and remained unchanged in the prefrontal cortex. No full-length canonical glucocorticoid response elements were identified in proximal promoter regions, although half-sites, candidate glucocorticoid receptor-binding sites, and distal atypical elements were detected.

Conclusion: Thus, 18 h after dexamethasone administration, stress-related behavior was selectively altered while spatial learning and locomotor activity remained preserved. These effects were accompanied by region-specific changes in corticosterone and activator protein 1 components, supporting context-dependent glucocorticoid transcriptional regulation across brain regions.

Keywords

dexamethasone; corticosterone; glucocorticoid receptor; stress-related behavior; AP-1; glucocorticoid response elements

Abbreviations

5-HIAA – 5-hydroxyindoleacetic acid; 5-HT – 5-hydroxytryptamine (serotonin); AP-1 – activator protein 1; AUC – area under the curve; BBB – blood–brain barrier; cDNA – complementary deoxyribonucleic acid; c-FOS – Fos proto-oncogene, AP-1 transcription factor subunit; c-JUN – Jun proto-oncogene, AP-1 transcription factor subunit; CNS – central nervous system; COMT – catechol-O-methyltransferase; CV – coefficient of variation; DA – dopamine; DEX – dexamethasone; DNA – deoxyribonucleic acid; DOPAC – 3,4-dihydroxyphenylacetic acid; EDTA – ethylenediaminetetraacetic acid; ELISA – enzyme-linked immunosorbent assay; FST – forced swim test; GAP-43 – growth-associated protein 43; GC – glucocorticoid; GR – glucocorticoid receptor; GRE – glucocorticoid response element; HPA axis – hypothalamic–pituitary–adrenal axis; HVA – homovanillic acid; IQR – interquartile range; MAOA – monoamine oxidase A; MAOB – monoamine oxidase B; mRNA – messenger ribonucleic acid; MWM – Morris water maze; NaCl – sodium chloride; NE – norepinephrine; NF-κB – nuclear factor kappa B; NIH – National Institutes of Health; NR3C1 – nuclear receptor subfamily 3 group C member 1; OF – open field test; PMSF – phenylmethylsulfonyl fluoride; PPIA – peptidylprolyl isomerase A; REML – restricted maximum likelihood; RIPA – radioimmunoprecipitation assay buffer; RNA – ribonucleic acid; RT-qPCR –

reverse transcription quantitative polymerase chain reaction; SDS – sodium dodecyl sulfate; STAT3 – signal transducer and activator of transcription 3; STAT5 – signal transducer and activator of transcription 5; TH – tyrosine hydroxylase; TPH1 – tryptophan hydroxylase 1; TPH2 – tryptophan hydroxylase 2; TSS – transcription start site

Introduction

Dexamethasone (DEX) is a synthetic glucocorticoid (GC) widely used in clinical practice because of its potent anti-inflammatory and immunosuppressive effects. At the same time, high doses of DEX can substantially alter central nervous system (CNS) function, including the activation of stress-reactivity mechanisms, the development of heightened emotional behavior, and impairment of cognitive processes (de Kloet et al. 2005; McEwen 2007; Gray et al. 2017), as GCs are major effectors of the neuroendocrine stress response. However, GC actions in the brain are heterogeneous and are determined by several additional factors, including hormone concentration and duration of exposure, as well as receptor density and region-specific features of intracellular signaling (Meijer et al. 2019; de Kloet et al. 1998). Therefore, acute high-dose DEX exposure may be regarded as a controlled perturbation of GC regulation that can be used to investigate adaptive and maladaptive CNS responses to altered GC signaling.

Monoaminergic systems represent an important effector component of this response. Dopamine, norepinephrine, and serotonin are involved in the regulation of emotional reactivity, motivation, stress-coping strategies, locomotor activity, learning, and memory (Baik 2020; Sara 2009; Cools et al. 2008). GCs can modulate monoamine synthesis, release, and catabolism; however, the direction and magnitude of these effects strongly depend on the intensity and duration of exposure (Rothschild et al. 1985; Inoue and Koyama 1996). Thus, region-specific remodeling of monoaminergic neurotransmission may represent one of the mechanisms linking alterations in GC signaling to behavioral responses.

In our previous study, we demonstrated that a single intraperitoneal administration of DEX at a dose of 8 mg/kg induces pronounced region-specific alterations in monoamine metabolism in the rat brain (Tiutiunnik et al. 2026). In the striatum, DEX administration increased dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) levels and decreased 5-HT levels; in the hippocampus, serotonin (5-HT) levels increased, whereas 5-hydroxyindoleacetic acid (5-HIAA) levels and the 5-HIAA/5-HT ratio decreased; in the prefrontal cortex, norepinephrine (NE), homovanillic acid (HVA), and 5-HIAA levels were reduced. These changes were accompanied by region-specific alterations in the expression of genes encoding enzymes involved in monoamine synthesis and catabolism (Tiutiunnik et al. 2026). We have also previously demonstrated structure-dependent alterations in neuron-specific proteins, including tyrosine hydroxylase and growth-associated protein 43 (GAP-43), as well as in calpain-2 proteolytic activity following DEX exposure (Tiutiunnik et al. 2025). Thus, even a single high-dose GC exposure induces a heterogeneous neurochemical response across different brain regions.

Aim

Accordingly, the aim of the present study was to determine whether the previously identified region-specific alterations in monoamine metabolism following a single

administration of DEX at 8 mg/kg are accompanied by changes in stress-related and emotional behavior, spatial learning and memory, and locomotor activity in rats, and to characterize the associated mechanisms of GC regulation.

Method

Animals

Adult male Wistar rats weighing (180 ± 20) g were used in all experiments. The rats were purchased from the Rappolovo nursery (Leningrad Region, Russia). The animals were housed in cages (4-5 animals/cage) in a room with controlled conditions (temperature of 24 ± 1°C, 45 – 65% humidity, and a 12 h light/12 h dark cycle). Chow in pellets and tap water were available *ad libitum* during the experimental period.

Experimental design

The experiment included 78 three-month-old male rats. The animals were assigned to two groups of equal size using block randomization.

Animals in the experimental group (DEX) received a single intraperitoneal injection of dexamethasone at a dose of 8 mg/kg. Animals in the control group (Control) received a single intraperitoneal injection of 1 mL of physiological saline.

Eighteen hours after administration, 40 animals were decapitated and 38 animals were underwent behavior tests (figure 1). Before decapitation, the rats were anesthetized by intraperitoneal injection of Zoletil 100® (35 mg/kg) and decapitated with a guillotine (Open-Science AE1601, RPC OpenScience Ltd, Russia). The rat brain was quickly excised and dissected from the skull according to methods previously described (Paul et al. 2008), and the striatum, hippocampus, and prefrontal cortex were sampled. Brain areas were identified with a brain atlas (Paxinos and Watson 2014).

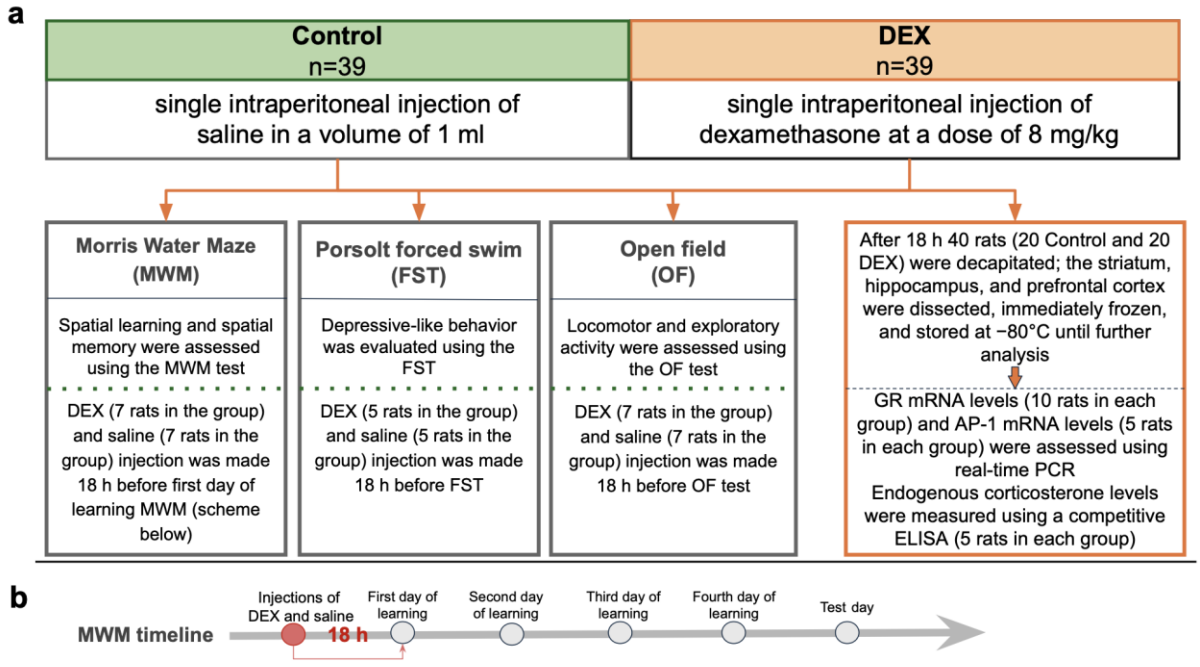


Fig. 1 Experimental design (a) and Morris water maze timeline (b)

Morris Water Maze Test

Spatial learning and memory were assessed using the Morris water maze test (MWM). The analysis was performed as previously described in our earlier study (Zubov et al. 2022).

To assess spatial learning and memory, the latency to locate the platform during each trial and the distance traveled were analyzed. During the probe trial, the time spent in the former platform location and the distance traveled within each of the four quadrants were also assessed.

For an integrated assessment of spatial learning dynamics, the area under the curve (AUC) was calculated for the latency to locate the platform across the consecutive training days. AUC values were calculated using the trapezoidal method based on the platform escape latency recorded during all trials on each training day. Higher AUC values reflected longer platform search times and, consequently, less efficient learning, whereas lower AUC values indicated improved acquisition of the spatial task. Comparison of AUC values across training days and experimental groups was used to assess the dynamics of spatial learning acquisition.

Forced Swim Test

The forced swim test (Porsolt test, FST) was performed over two consecutive days. On the first day, the animals underwent a 15-min forced swimming session (pretest) in cylindrical glass containers 40 cm in height and 25 cm in diameter, filled with water to a depth of 30 cm. The water temperature was maintained at 25 ± 1°C.

Twenty-four hours after the pretest, the rats underwent a 5-min test session. The durations of immobility (passive swimming) and active swimming were measured in seconds.

Open Field Test

The open field (OF) test was performed in a circular arena 100 cm in diameter with 42-cm-high walls and a double-layer floor containing 16 holes, each 2 cm in diameter. The duration of the test was 10 min for each animal.

One hour before testing, the animals were transferred to the room containing the experimental apparatus for acclimatization. Testing was performed during the evening period between 18:00 and 22:00. After each animal was tested, the floor of the arena was sequentially cleaned with a 0.6% hydrogen peroxide solution, rinsed with water to remove residual hydrogen peroxide, and wiped dry to eliminate olfactory cues.

Immediately before the test, each rat was placed in the center of the arena. Behavior was video-recorded using a Logitech C525 camera (Switzerland) positioned 100 cm above the center of the arena, followed by offline video analysis.

The total distance traveled during the test was used as an indicator of locomotor activity. Behavioral analysis was performed using the original software “Program for the Study of Behavior of Small Laboratory Animals” (PIPMLG-1, Tracking), developed by researchers from the Research Institute of Occupational Medicine in collaboration with the Pavlov Department of Physiology, Institute of Experimental Medicine. The software is registered in the Russian Register of Computer Programs (Certificate of State Registration No. 2016619940, dated September 1, 2016).

Enzyme-linked immunosorbent assay for corticosterone

To minimize the influence of circadian rhythm variations, all animals were decapitated, and blood and brain samples were collected between 9:00 and 11:00 AM. Sample collection in the DEX and Control groups was scheduled within the same circadian window.

The tissue samples were homogenized in 200 µL of RIPA buffer (10 mM Tris, 1 mM EDTA, 140 mM NaCl, 0.1% SDS, 1% Triton-X100, 1 mM PMSF) and centrifuged at 8500×g for 20 min. The supernatants were stored at -80°C until analysis.

Corticosterone concentrations in brain samples were measured using a commercial enzyme-linked immunosorbent assay kit (CORT(Corticosterone) ELISA Kit, EU3108, Wuhan Fine Biotech Co., Ltd, China). The assay was performed according to the manufacturer's instructions. Corticosterone concentrations were calculated using a 4-parameter logistic curve fit. The sensitivity of the assay was 1,688 ng/ml, CV (%) - 6,32, data are presented as ng (corticosterone)/ml.

RNA isolation

Total mRNA was isolated from frozen tissues (50-100 mg) using the ExtractRNA kit (#BC032, Evrogen, Russia) following the manufacturer's protocols for Phenol–chloroform extraction. Briefly, after two chloroform extraction steps, RNA was precipitated with isopropanol and the pellet was washed twice with 70% ethanol. After air-drying, RNase Free water (#W4502, Sigma) was added to each sample in a volume of 20 µl. The concentrations of RNA samples were determined using a NanoDrop2000 spectrophotometer (Thermo Scientific, USA), and the purity was verified by confirming that each sample had an A260/A280 optical density ratio >1.9. After that, the samples were stored at -80°C until further analysis.

Reverse transcription

A total of 2 µg mRNA was used for complementary DNA (cDNA) synthesis. The reverse transcription reaction was performed using a commercial Reverta reagent kit (#SK022S, Evrogen, Russia) according to the manufacturer's instructions. The resulting cDNA was stored at -20 °C for further use.

Quantitative real-time PCR

Reverse transcription quantitative PCR (RT-qPCR) was performed using the Bio-Rad CFX96 Real-Time System (Bio-Rad Laboratories, USA) and a commercial qPCRmix-HS SYBR 5x reagent kit (#PK147L, Evrogen, Russia). Primers were designed using Primer-BLAST (NCBI, USA). The optimal reaction parameters were determined for each primer to ensure successful amplification. A list of primer sequences is provided in Supplementary File 1. The PCR protocol commenced with an initial denaturation at 95°C for 5 minutes, subsequently comprising 45 cycles each consisting of a 20-second denaturation (94°C), a 40-second annealing (60°C), and a 50-second extension (72°C). A melting curve analysis was conducted, gradually increasing the temperature from 65°C to 95°C in 0.5°C steps, to evaluate the specificity of the amplification process. For normalization purposes, the expression of Peptidyl prolyl isomerase A (PPIA) and Phosphoglycerate kinase 1 (PGK1) genes were chosen as reference genes, the expression of which is stable in the brain regions under study

(Tiutiunnik et al. 2026). To quantify relative gene expression (only GR mRNA expression), we employed the method described previously (Vandesompele et al. 2002), with results displayed as arbitrary units in the graphs. Quantile normalization was used to normalize the batch effect in the PCR data (Mar et al. 2009).

In silico analysis of glucocorticoid response elements

Potential GR-dependent regulation of *TH, MAOA, MAOB, TPH1, TPH2,* and *COMT* was assessed *in silico*. For human and rat genes, the proximal −300-bp promoter region and the first exon were analyzed using MANE Select and RefSeq Select transcripts, respectively (Morales et al. 2022; Goldfarb et al. 2025). Canonical and GRE-like sequences, GRE half-sites, and NR3C1-binding motifs were identified using the JASPAR MA0113.3 matrix with a relative score threshold of 0.80 (Castro-Mondragon et al. 2022). For *TH, MAOA,* and *MAOB*, extended promoter regions containing previously characterized GR-responsive elements were additionally analyzed.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 11.0 (GraphPad Software, USA). Data are presented as individual experimental points with median values in the figures and as median and interquartile range (IQR) in the Results section. Differences between two independent groups were analyzed using the Mann–Whitney U test. The corresponding Mann–Whitney U statistics are reported in the Results section. A p-value <0.05 was considered statistically significant.

The dynamics of learning in the Morris water maze were analyzed using a repeated-measures mixed-effects model fitted by restricted maximum likelihood (REML). Group (Control and DEX) was included as a between-subject factor, whereas training day was included as a within-subject repeated-measures factor. The model accounted for repeated measurements obtained from the same animal across training days and was used to assess the main effects of group and training day, as well as the **group×day** interaction. When appropriate, the Geisser–Greenhouse correction was applied. Multiple comparisons were performed using Sidak's post hoc test.

Ethics approval

All experiments were performed in accordance with institutional guidelines and the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals as well as national laws (Ministry of Health of the Russian Federation N267, June 19, 2003; Guide for the Use of Laboratory Animals, Moscow, 2005) and permission of the Local Ethical Committee for this research Federal State Budgetary Scientific Institution "Institute of Experimental Medicine" of St. Petersburg № 2/23 from 15.06.2023.

Results

Stress-related behavior, spatial learning and locomotor activity

In the forced swim test, rats in the DEX group showed a decrease in active swimming time compared with the Control group: 61.48 s (58.70; 71.05) versus 85.38 s (76.10; 116.9), U

= 2; p = 0.0317. At the same time, immobility time increased in the DEX group: 95.28 s (78.08; 105.3) versus 58.31 s (20.03; 80.18), U = 2; p = 0.0317. The data are presented in Figure 2.

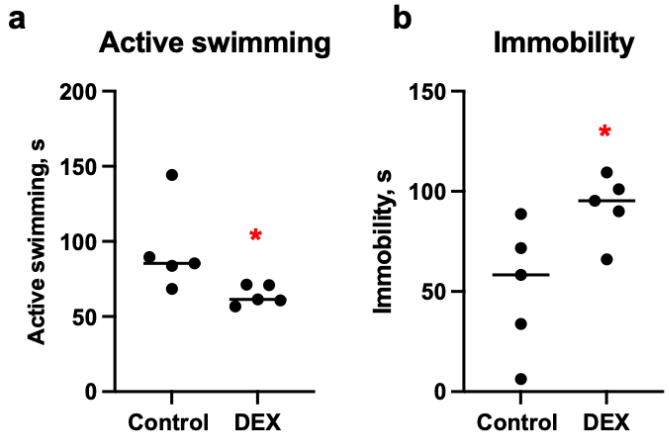


Fig. 2 Forced swim test. Effect of a single administration of DEX at a dose of 8 mg/kg on active swimming time (a) and immobility time (b). Data are presented as individual experimental points and median values; each group included 5 animals. *p < 0.05 compared with the Control group. Mann–Whitney U test

During training in the MWM, the latency to reach the platform gradually decreased in both the Control and DEX groups (Figure 3a). Analysis using a mixed-effects model revealed a significant effect of training day (p < 0.0001), indicating the formation of a spatial learning skill in both groups. However, no significant effect of the group was detected (p = 0.9650), nor was there a significant group × day interaction (p = 0.3100).

Pairwise comparisons between groups on each training day revealed no significant differences between dexamethasone-treated and control animals. On day 1, the latency to reach the platform was 51.4 s in the DEX group and 58.0 s in the Control group (p = 0.8696); on day 2, 32.6 s and 20.9 s, respectively (p = 0.4395); on day 3, 10.1 s and 16.1 s (p = 0.9013); and on day 4, 15.0 s and 13.6 s (p = 0.9995). The data are presented in Figure 3a.

AUC, reflecting the total time required to reach the platform during a training day, progressively decreased in both control animals and dexamethasone-treated animals. The mixed-effects model revealed a significant effect of training day on AUC values ($F(3,4) = 28.95$; p = 0.00358), whereas the effects of group ($F(1,4) = 0.2398$; p = 0.6268) and group × day interaction ($F(3,4) = 0.3217$; p = 0.8097) were not significant.

In the DEX group, AUC on day 2 was lower than on day 1 (−74.9; 95% CI: −136.9 to −12.8; p = 0.0108). On day 3, AUC was lower than on day 1 (−137.5; 95% CI: −199.6 to −75.43; p < 0.0001) and day 2 (−62.6; 95% CI: −124.7 to −0.5602; p = 0.0469). On day 4, AUC also remained lower than on day 1 (−123.3; 95% CI: −185.4 to −61.22; p < 0.0001), but did not differ from days 2 and 3 (p = 0.2033 and p = 0.9894, respectively).

In the Control group, AUC also decreased on day 2 compared with day 1 (−99.0; 95% CI: −166.0 to −31.91; p = 0.0012), while on days 3 and 4 it remained lower than on day 1 (−133.9; 95% CI: −201.0 to −66.9; p < 0.0001, and −140.3; 95% CI: −207.4 to −73.31; p < 0.0001, respectively). No significant differences were detected between days 2, 3, and 4 in the Control group (p > 0.05).

Comparison between groups within each training day revealed no significant differences: AUC values in the DEX group did not differ from those in the Control group on days 1, 2, 3, or 4. Thus, a single administration of dexamethasone did not alter the overall dynamics of spatial skill acquisition, as assessed by the area under the learning curve in the MWM (Figure 3b).

The percentage of time spent in the target quadrant also did not differ significantly between the Control and DEX groups. In the Control group, this parameter was 31.84% (21.0; 39.2), whereas in the DEX group it was 33.10% (28.9; 38.1) (U = 22; p = 0.8048) (Figure 3c).

In the MWM, no significant differences between the Control and DEX groups were found in the total distance traveled. The total distance traveled was 18.8 m (18.5; 19.4) in the Control group and 17.4 m (15.9; 19.6) in the DEX group (U = 18; p = 0.4557) (Figure 3d).

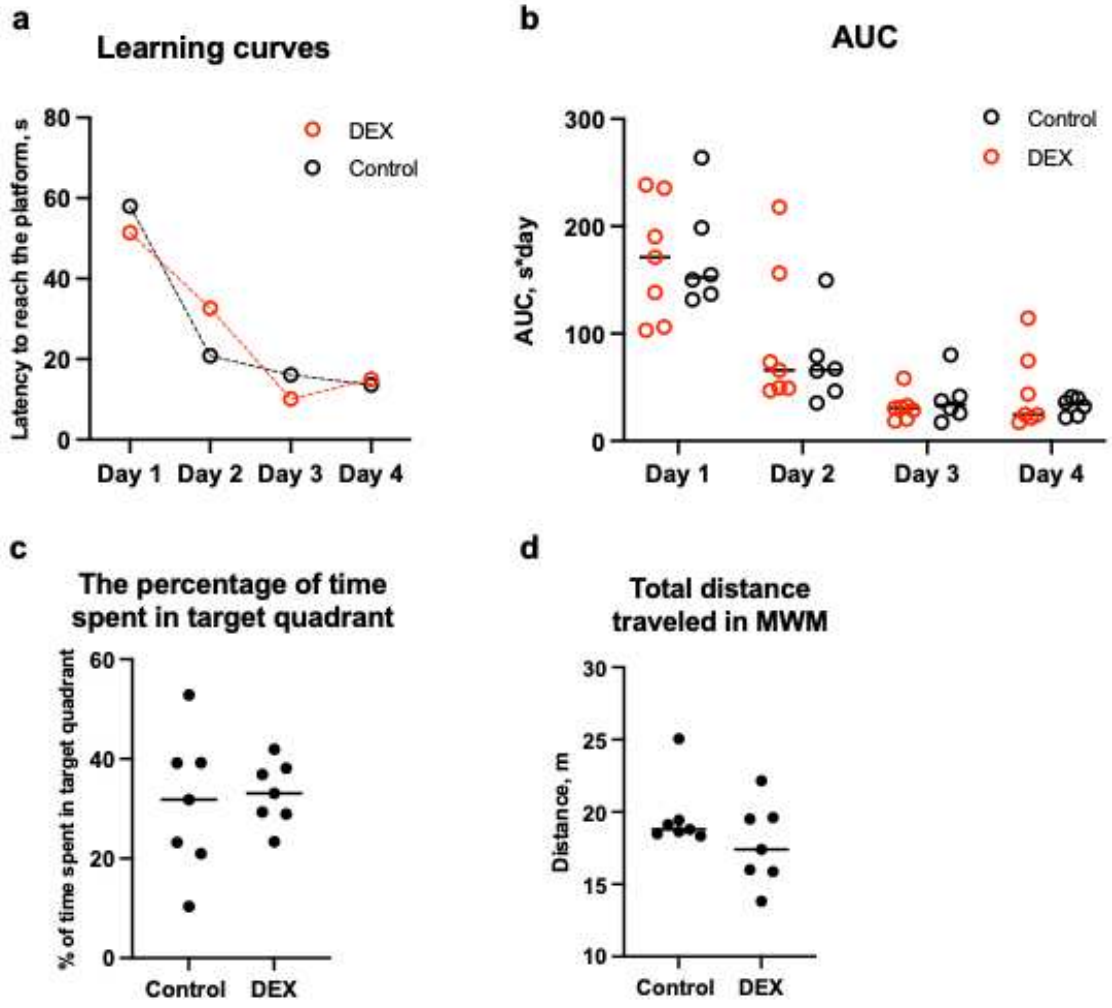


Fig. 3 Morris water maze test. Effect of a single administration of DEX at a dose of 8 mg/kg on spatial learning and memory: learning dynamics across training days (a); area under the learning curve (AUC) for each rat in the Control and DEX groups (b); percentage of time spent in the target quadrant during the probe trial (c); total distance traveled during the probe trial (d). For visualization, data points in panel (a) are connected by lines. Data are presented as individual experimental points (b–d) and median values (a–d); each group included 7 animals. Statistical analysis was performed using a mixed-effects model for repeated measures with Sidak's post hoc test for panels (a, b) and the Mann–Whitney U test for panels (c, d)

Since performance in the MWM depends not only on spatial learning and memory but also on the general locomotor activity of the animal, the open field test was additionally performed. This made it possible to determine whether the observed behavioral features were associated with altered locomotor activity after DEX administration.

In the open field test, no significant differences were observed between the DEX and Control groups in the total distance traveled: 12.44 m (10.42; 15.93) versus 12.50 m (9.25; 15.95), $U = 24$; $p > 0.9999$. Likewise, no significant differences were found in the total duration of locomotor activity: 8.10 s (7.28; 14.22) versus10.48 s (7.08; 13.09), $U = 22$; $p = 0.7780$. The data are presented in Figure 4a, 4b.

To additionally assess the emotional component of behavior in the open field test, the total duration of freezing and grooming was analyzed, since these parameters reflect passive defensive responses and features of stress-induced behavior in animals. In the DEX group, the total duration of freezing increased compared with the Control group: 12.12 s (7.00; 18.00) versus 3.00 s (0.99; 5.00), $U = 3$; $p = 0.0041$. At the same time, the total duration of grooming decreased: 8.29 s (6.00; 10.00) versus 16.99 s (16.21; 29.09), $U = 1$; $p = 0.0012$. The data are presented in Figure 4c, 4d.

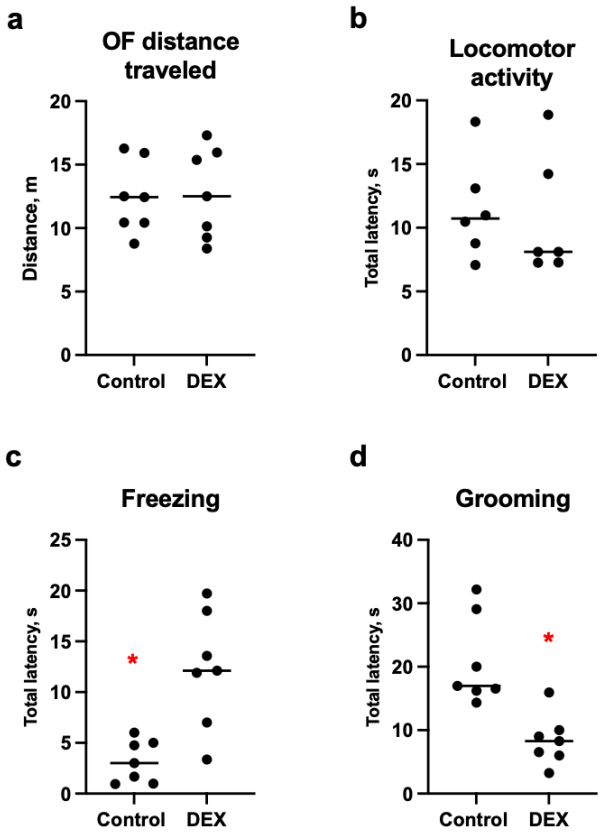


Fig. 4 Open field test. Effect of a single administration of DEX at a dose of 8 mg/kg on total distance traveled (a), locomotor activity (b), total duration of freezing (c), and grooming (d). Data are presented as individual experimental points and median values; each group included 7 animals. *$p < 0.05$ compared with the Control group. Mann–Whitney U test

GR mRNA expression and corticosterone levels

In the hippocampus, no significant differences in GR mRNA expression was found between the Control and DEX groups. GR mRNA expression was 0.03 (−1.08; 1.10) in the Control group and −0.05 (−0.75; 0.43) in the DEX group ($U = 48$; $p > 0.05$).

In the striatum, no significant differences in GR mRNA expression was found between the Control and DEX groups. GR mRNA expression was 0.05 (−0.31; 0.70) in the Control group and −0.46 (−0.87; 0.01) in the DEX group ($U = 29$; $p > 0.05$).

In the prefrontal cortex, no significant differences in GR mRNA expression was found between the Control and DEX groups. GR mRNA expression was −0.59 (−0.91; −0.19) in the Control group and 0.42 (−0.38; 1.15) in the DEX group ($U = 28$; $p > 0.05$). The data are presented in Figure 5.

Negative mRNA values resulted from quantile normalization followed by data centering. With this type of processing, expression values are adjusted to a common distribution and may be presented on a scale in which zero corresponds to the conditional mean level, whereas positive and negative values reflect relative deviations from this level. Thus, negative values do not have independent biological meaning but indicate expression levels below the sample mean.

To evaluate the effect of a single administration of dexamethasone at a dose of 8 mg/kg on endogenous corticosterone levels in the hippocampus, striatum, and prefrontal cortex, ELISA was performed.

In the hippocampus, no differences in corticosterone levels were found between the Control and DEX groups. Corticosterone levels were 27.4 ng/mL (26.9; 30.8) in the Control group and 25.5 ng/mL (21.4; 32.0) in the DEX group ($U = 7$; $p = 0.8857$).

In the striatum, corticosterone levels were decreased in the DEX group compared with the Control group. Corticosterone levels were 30.1 ng/mL (25.4; 33.8) in the Control group and 19.7 ng/mL (16.4; 21.8) in the DEX group ($U = 0$; $p = 0.0079$).

A similar result was observed in the prefrontal cortex. In the DEX group, corticosterone levels were lower than in the Control group. Corticosterone levels were 29.2 ng/mL (25.3; 31.8) in the Control group and 23.0 ng/mL (19.2; 24.0) in the DEX group ($U = 0$; $p = 0.0286$). The data are presented in Figure 5.

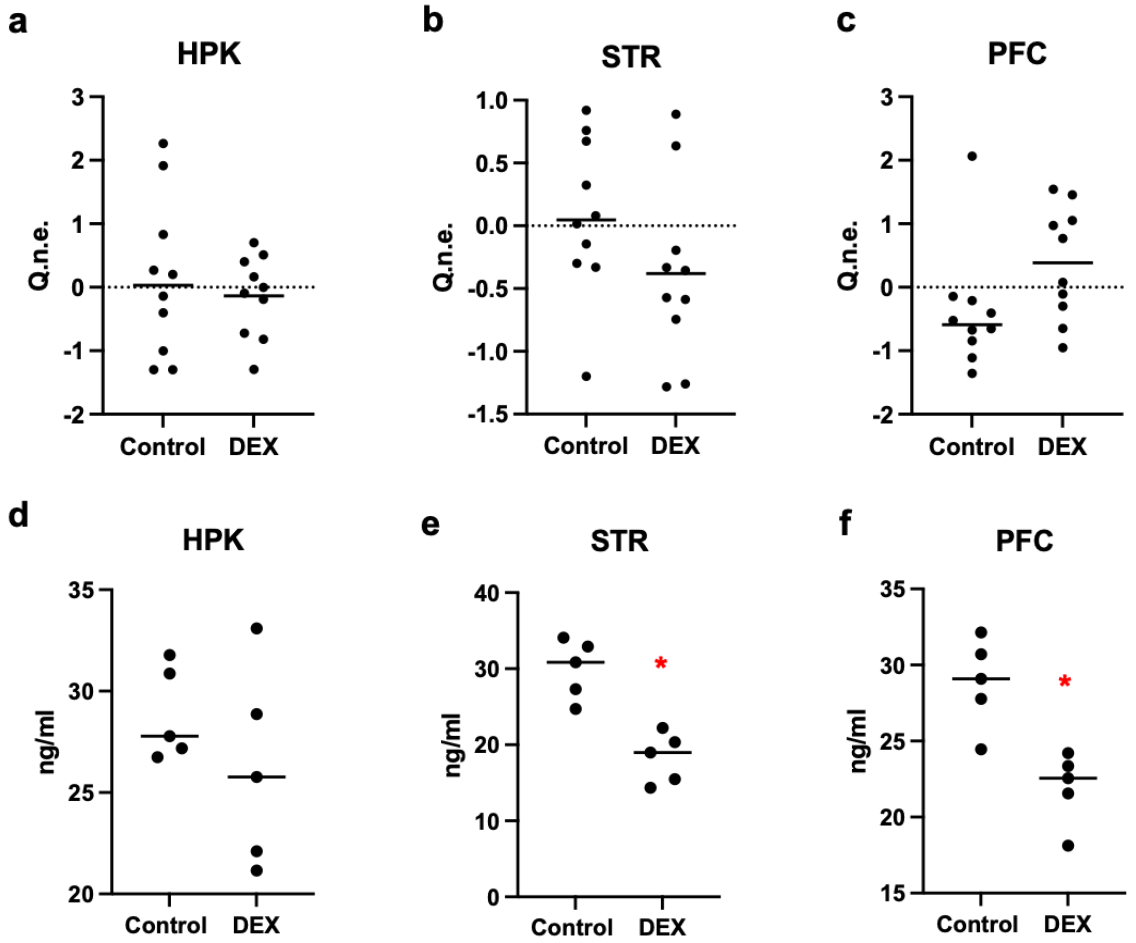


Fig. 5 Effect of a single administration of DEX at a dose of 8 mg/kg on GR mRNA expression and endogenous corticosterone levels in different brain regions. GR mRNA expression in the hippocampus (a), striatum (b), and prefrontal cortex (c); endogenous corticosterone levels in the hippocampus (d), striatum (e), and prefrontal cortex (f). Data are presented as individual experimental points and median values. Each group included 10 animals for GR mRNA analysis (a–c) and 5 animals for corticosterone measurements (d–f). Q.n.e., quantile-normalized expression. *p < 0.05 compared with the Control group. Mann–Whitney U test

Jun and Fos mRNA expression

In the hippocampus, c-JUN mRNA expression was significantly increased in the DEX group compared with the Control group: 7.0 (4.1; 10.3) versus 0.56 (0.2; 1.1), respectively (U = 0; p = 0.0079). In contrast, in the striatum, c-JUN mRNA expression was significantly decreased following dexamethasone administration: 0.3 (0.2; 0.5) in the DEX group versus 1.0 (0.8; 1.8) in the Control group (U = 0; p = 0.0079). In the prefrontal cortex, no significant differences in c-JUN mRNA expression was observed between the groups: 0.4 (0.03; 0.53) in the DEX group and 0.6 (0.4; 1.2) in the Control group (U = 5; p = 0.1508).

A similar region-specific pattern was observed for c-FOS mRNA. In the hippocampus, c-FOS mRNA expression was significantly higher in the DEX group than in the Control group: 2.5 (2.1; 3.0) versus 0.6 (0.2; 1.1), respectively (U = 0; p = 0.0079). In the striatum, c-FOS mRNA expression was significantly lower in the DEX group: 0.7 (0.6; 0.7) compared with 1.2 (1.0; 1.4) in the Control group (U = 0; p = 0.0079). No significant differences in c-FOS mRNA

expression was detected in the prefrontal cortex: 1.1 (0.1; 3.3) in the DEX group versus 0.9 (0.3; 5.1) in the Control group (U = 11; p = 0.8413). The data are presented in Figure 6.

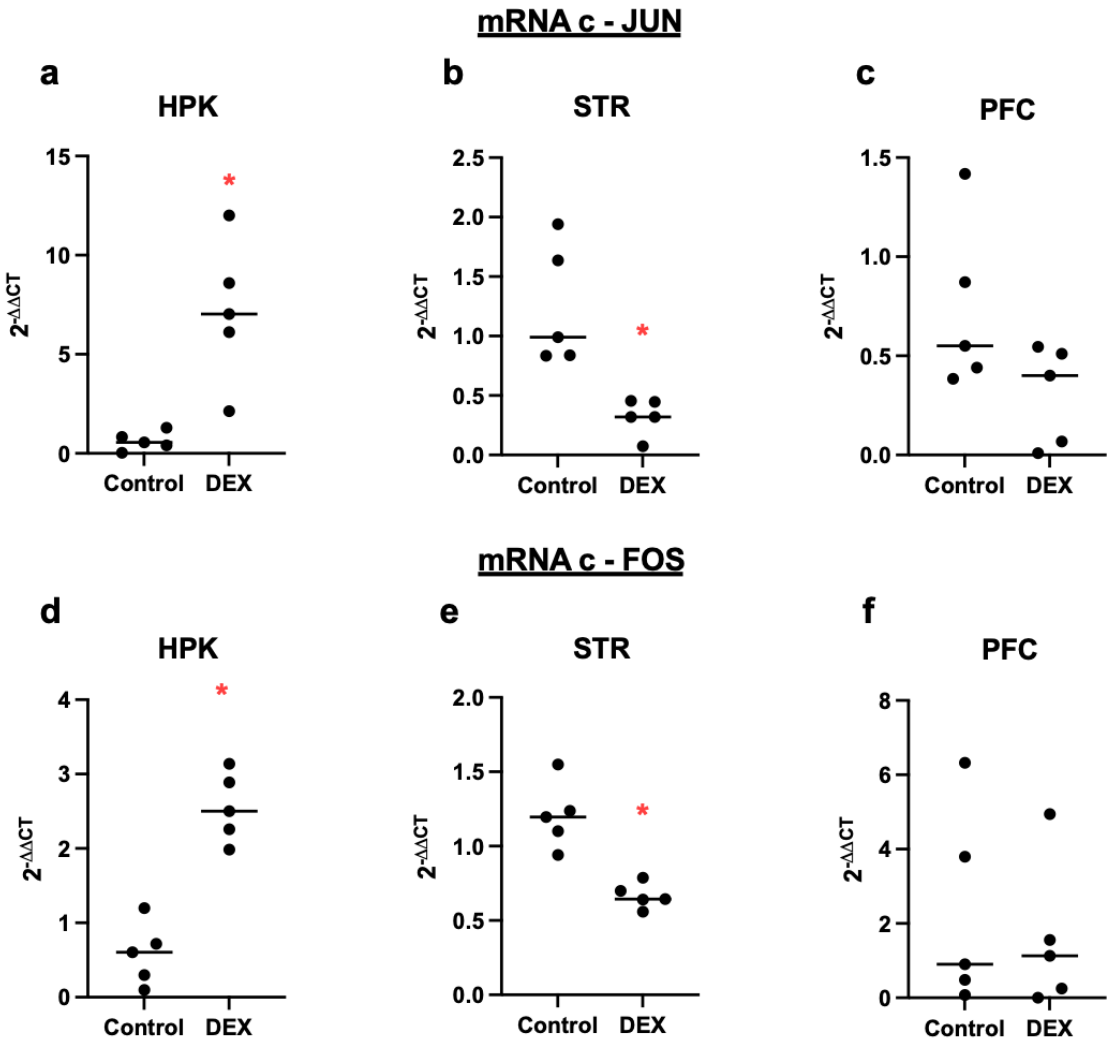


Fig. 6 Effect of a single administration of DEX at a dose of 8 mg/kg on c-JUN and c-FOS mRNA expression in the rat brain. c-JUN mRNA expression in the hippocampus (a), striatum (b), and prefrontal cortex (c); c-FOS mRNA expression in the hippocampus (d), striatum (e), and prefrontal cortex (f). The y-axis represents relative gene expression ($2^{-\Delta\Delta CT}$). Data are presented as individual experimental points and median values; each group included 5 animals. *p < 0.05 compared with the Control group. Mann–Whitney U test

In silico analysis of candidate glucocorticoid response elements

No full-length canonical GREs or GRE-like sequences of the predefined type were identified within the proximal regulatory regions of the analyzed genes involved in monoamine metabolism. Individual GRE half-sites were detected in the promoter regions of human *TPH2* (TGTTCT, −191 to −186) and rat *Comt* (AGAACA, −175 to −170). When the JASPAR NR3C1 matrix MA0113.3 was used, putative GR-binding sites were identified in the promoter regions of human *MAOA* (−289 to −273) and human *COMT* (−164 to −148). No corresponding sites meeting the selected threshold were identified in the rat genes. Because isolated half-sites and matches to a transcription factor binding matrix do not by themselves demonstrate direct interaction with GR, these sequences were considered computational candidates.

Additional analysis of more extended promoter regions revealed the experimentally characterized atypical TGACTAA element in the human *TH* and rat *Th* genes. Relative to the transcription start sites of the selected reference transcripts, this element was located at −7240 to −7234 in human *TH* and at −5753 to −5747 in rat *Th*. Within the extended 2-kb promoter region of human *MAOA*, two AGAACA half-sites were identified at −1307 to −1302 and −1271 to −1266; the previously identified PWM candidate at −289 to −273 was also located within this interval. An additional PWM candidate was detected in the 2-kb promoter region of human *MAOB* at −1795 to −1779.

However, unambiguous assignment of the identified *MAOA* and *MAOB* sequences to the experimentally described GRE/ARE3 and GRE4 elements requires separate alignment of the original promoter constructs with the current reference genomic sequences. Thus, the absence of canonical GREs within the proximal −300-bp region does not exclude the involvement of more distal, atypical, or composite regulatory elements in GR-mediated transcriptional regulation. The procedure for this analysis is provided in Supplementary File 2.

Discussion

High-dose GC exposure can substantially alter central nervous system function; however, the nature of these effects depends on the intensity and duration of hormonal exposure as well as on the specific characteristics of individual brain regions (Gray et al. 2017; Inoue and Koyama 1996). In the present study, a single administration of DEX at a dose of 8 mg/kg predominantly affected emotional and stress-related behavior (Figures 2, 4), whereas no pronounced deficits in spatial learning, memory, or general locomotor activity were observed (Figures 3, 4). These functional changes were accompanied by region-specific alterations in endogenous corticosterone levels (Figure 5d–f) and in the expression of AP-1 components (Figure 6), whereas GR mRNA expression (Figure 5) remained unchanged in all examined brain regions. Taken together, these findings indicate that acute high-dose GC exposure induces a region-dependent rather than generalized CNS response, characterized primarily by alterations in emotional and stress-related behavior while learning and memory remain relatively preserved.

The behavioral effects were selective. In the MWM, DEX did not affect the dynamics of spatial learning or probe-trial performance (Figure 3). Similarly, the absence of changes in total distance traveled and locomotor activity in the OF test argues against nonspecific suppression of motor activity. At the same time, DEX administration increased immobility in the FST and freezing duration in the open field, whereas active swimming and grooming were reduced. According to the current interpretation of the FST, increased immobility and reduced active swimming should not be regarded exclusively as manifestations of depression-like behavior but rather as alterations in the strategy used to cope with an acute inescapable stressor. Within this framework, immobility can be interpreted as a passive coping response, whereas active swimming reflects a more active behavioral response to the stressful situation (Commons et al. 2017; Molendijk and de Kloet 2019).

The behavioral profile observed in the present study differs from the effects reported after repeated DEX administration. Daily administration of DEX at 1.5 mg/kg for 21 days has previously been associated not only with emotional disturbances but also with impaired spatial learning and memory (Laaziz et al. 2022b; Laaziz et al. 2022a). In addition, in a five-day DEX-

induced insulin resistance model (1 mg/kg/day), reduced grooming was accompanied by decreased locomotor activity (Çalışkan and Karabulut 2025). In the present study, reduced grooming was observed in the absence of impaired locomotor activity. This suggests that the reduction in grooming reflects altered organization of stress-related behavior rather than nonspecific motor suppression. More broadly, the differences between acute and repeated DEX exposure are consistent with the nonlinear and time-dependent nature of the GC response, whereby short-term high-dose exposure and prolonged GR stimulation may engage different adaptive and maladaptive regulatory mechanisms.

These findings are of particular interest in view of the alterations in monoamine metabolism that we previously identified following administration of the same DEX dose (Tiutiunnik et al. 2026). Region-specific alterations in dopaminergic, noradrenergic, and serotonergic systems may provide a neurochemical basis for the changes in stress reactivity and emotional behavior observed in the present study. At the same time, the absence of impaired spatial learning indicates that alterations in monoaminergic neurotransmission do not necessarily result in simultaneous disruption of all functions associated with the corresponding brain regions. Rather, the response to acute GC exposure appears to manifest primarily as a shift in behavioral strategy under stressful conditions, whereas cognitive deficits may emerge following more prolonged or repeated GC exposure.

The absence of changes in GR mRNA levels in the hippocampus, striatum, and prefrontal cortex does not exclude the involvement of the GR in mediating the observed behavioral effects.

The molecular effects of DEX are primarily mediated through activation of GR. Following ligand binding, GR becomes activated, translocates to the nucleus, and regulates transcription of target genes (Oakley and Cidlowski 2013). The classical genomic mechanism involves GR binding to GREs within regulatory DNA regions (Oakley and Cidlowski 2013). However, the transcriptional actions of GR are not limited to classical GREs. Activated GR can functionally interact with other transcription factors, including AP-1 and NF-κB (Kassel and Herrlich 2007); interactions with STAT3 and STAT5 have also been described (Langlais et al. 2012; Lechner et al. 1997). In the present study, particular attention was given to AP-1 because its JUN and FOS components participate in stress-induced transcriptional responses and can functionally interact with GR. The outcome of GR–AP-1 interaction depends on the cellular and regulatory context and may lead to different transcriptional responses. Such a mechanism may contribute to the region-specific response of the brain to the same GC stimulus.

An additional important finding was the region-specific alteration in endogenous corticosterone levels following DEX administration.

DEX affects hypothalamic–pituitary–adrenal (HPA) axis function through negative feedback and may therefore alter endogenous corticosterone levels (Cole et al. 2000). Consequently, the effects of DEX in different brain regions may reflect a combination of direct GR activation by the synthetic GC, alterations in endogenous GC signaling, and region-specific features of GR-dependent transcriptional regulation. Simultaneous analysis of corticosterone, GR expression, and AP-1 components enables these processes to be assessed at several levels of the same regulatory system.

Following DEX administration, corticosterone levels were reduced in the striatum and prefrontal cortex but remained unchanged in the hippocampus. A decrease in endogenous GC levels is an expected consequence of negative feedback following GR activation by synthetic GC. Indeed, DEX is widely used in suppression tests because of its ability to reduce HPA-axis activity and, consequently, circulating GC levels. In rats, administration of DEX at 50 μg/kg suppressed the stress-induced increase in corticosterone by approximately 80%, an effect attributed predominantly to GR-dependent inhibition at the pituitary level (Cole et al. 2000). However, corticosterone changes differed among the examined brain regions, indicating a region-specific response to DEX administration. This is consistent with the concept of regional heterogeneity in GC signaling, which is determined by the combined effects of hormonal exposure, cellular composition, receptor context, and local organization of intracellular signaling pathways (Gray et al. 2017; Meijer et al. 2019).

Importantly, changes in endogenous corticosterone did not parallel those in c-JUN and c-FOS. In the hippocampus, where corticosterone levels remained unchanged, mRNA levels of both AP-1 components were increased. In the striatum, reduced corticosterone was accompanied by decreased c-JUN and c-FOS expression, whereas in the prefrontal cortex reduced corticosterone was not accompanied by significant changes in either transcript. This dissociation makes it unlikely that the regional transcriptional response can be explained solely by changes in endogenous corticosterone. Rather, it may result from direct activation of GR by administered DEX in combination with local features of intracellular and transcriptional regulation.

One potential mechanism underlying such regulation involves the interaction of activated GR with GREs. However, the results of the *in silico* analysis indicate that potential GR-dependent regulation of *TH, MAOA, MAOB, TPH1, TPH2,* and *COMT* cannot be reduced solely to the presence of a classical GRE immediately upstream of the transcription start site. No full-length canonical GREs were detected within the standardized proximal −300 bp interval, whereas GRE half-sites and potential sites matching the NR3C1 binding matrix were identified for individual genes. Moreover, extended analysis revealed a more distal atypical GRE within the regulatory region of *TH*. These findings should be interpreted as identifying potential regulatory regions rather than demonstrating direct GR binding.

The absence of classical GREs in the proximal promoter does not exclude GR-dependent regulation. A substantial proportion of functional GR-binding sites have been shown to occur more than 10 kb from the transcription start site (So et al. 2007), and GR can bind individual GRE half-sites as a monomer and regulate specific target genes (Schiller et al. 2014). GR-dependent transcription can also involve composite regulatory elements containing binding sites for other transcription factors. In particular, a composite element has been described in the *CRH* promoter in which adjacent GR- and AP-1-binding sites are required for GC-dependent transcriptional repression (Malkoski and Dorin 1999).

GR–AP-1 interactions are context-dependent and may result in transcriptional repression or cooperative regulation depending on the cellular context and organization of the regulatory locus (Oakley and Cidlowski 2013; Mifsud et al. 2021). Therefore, the observed alterations in c-JUN and c-FOS mRNA levels are of interest as indicators of remodeling of the AP-1-associated transcriptional system following DEX administration. However, changes in

these transcripts alone do not establish altered AP-1 activity, which would require assessment of protein abundance, phosphorylation, dimerization, and/or DNA-binding activity.

Nevertheless, the coordinated regional pattern of c-JUN and c-FOS changes is noteworthy. Both transcripts were increased in the hippocampus, decreased in the striatum, and remained unchanged in the prefrontal cortex. Thus, c-JUN and c-FOS responses showed a pronounced region-specific pattern, with opposite changes in the hippocampus and striatum and no significant response in the prefrontal cortex. Such heterogeneity is consistent with previous evidence demonstrating brain-region-specific transcriptional responses to DEX (Gerstner et al. 2022). This may be particularly relevant to the hippocampus, where acute stress has been shown to induce dynamic changes in GR binding to chromatin accompanied by transcriptional alterations (Mifsud et al. 2021). Accordingly, increased c-JUN and c-FOS expression in the absence of changes in GR mRNA may reflect an altered functional state of a GR-dependent transcriptional network rather than changes in receptor abundance itself.

The absence of impaired spatial learning despite pronounced transcriptional changes in the hippocampus is not necessarily contradictory. Molecular remodeling following acute hormonal exposure may precede the emergence of functional deficits or may represent a compensatory response. Under the present experimental conditions, increased c-JUN and c-FOS expression may reflect an early adaptive response to GC stimulation, whereas the development of cognitive impairment may require more prolonged exposure. This interpretation is consistent with studies of repeated DEX administration, in which impairment of spatial learning and memory in the Morris water maze was observed after 21 days of treatment (Laaziz et al. 2022b; Laaziz et al. 2022a).

Overall, a single high dose of DEX induces a reorganization of the GC stress response that is functionally manifested primarily by alterations in stress-related and emotional behavior while spatial learning and general locomotor activity remain preserved. This response develops without changes in GR mRNA levels but is accompanied by region-specific alterations in endogenous corticosterone and bidirectional changes in c-JUN and c-FOS expression. Together with the *in silico* findings, these results suggest the involvement of both GRE-dependent and context-dependent GR/AP-1-associated mechanisms.

Limitations

The present study has several limitations. GC signaling was assessed predominantly at the transcriptional level. GR was evaluated based on its mRNA level, which does not provide direct information on receptor protein abundance, phosphorylation status, nuclear translocation, or functional activity. Similarly, changes in c-JUN and c-FOS mRNA levels reflect remodeling of the AP-1-associated transcriptional system but do not provide direct evidence of altered AP-1 activity. In addition, the *in silico* GRE analysis identifies only potential regulatory regions and does not demonstrate actual GR binding to DNA *in vivo*. Further studies should therefore assess GR protein abundance and subcellular localization, JUN and FOS protein levels and/or activity, and direct GR binding to regulatory regions using approaches such as chromatin immunoprecipitation-based methods.

Conclusion

Under the present experimental conditions, a single high dose of DEX was associated with changes in stress-related behavior, whereas no statistically significant differences were detected in spatial learning, memory, or general locomotor activity. These findings were accompanied by region-specific changes in endogenous corticosterone and c-JUN and c-FOS mRNA levels, with no significant differences in GR mRNA expression between groups. The *in silico* analysis identified candidate regulatory sequences associated with monoamine-related genes, although their functional significance and involvement in GR-mediated regulation remain to be established. Overall, these observations are consistent with a region-dependent response to acute high-dose DEX and support further investigation of the possible contribution of GR- and AP-1-associated transcriptional mechanisms.

References

1. Baik JH (2020) Stress and the dopaminergic reward system. Experimental & Molecular Medicine 52(12):1879–1890. https://doi.org/10.1038/s12276-020-00532-4. PMID: 33257725.
2. Çalışkan H, Karabulut G (2025) Effects of the dexamethasone-induced insulin resistance model on self-care behaviors and brain-derived growth factor in rats. Journal of Endocrinology 265(3):e250088. https://doi.org/10.1530/JOE-25-0088. PMID: 40327055.
3. Castro-Mondragon JA, Riudavets-Puig R, Rauluseviciute I, Berhanu Lemma R, Turchi L, Blanc-Mathieu R, et al (2022) JASPAR 2022: the 9th release of the open-access database of transcription factor binding profiles. Nucleic Acids Research 50(D1):D165–D173. https://doi.org/10.1093/nar/gkab1113. PMID: 34850907.
4. Cole MA, Kim PJ, Kalman BA, Spencer RL (2000) Dexamethasone suppression of corticosteroid secretion: evaluation of the site of action by receptor measures and functional studies. Psychoneuroendocrinology 25(2):151–167. https://doi.org/10.1016/S0306-4530(99)00045-1. PMID: 10674279.
5. Commons KG, Cholanians AB, Babb JA, Ehlinger DG (2017) The rodent forced swim test measures stress-coping strategy, not depression-like behavior. ACS Chemical Neuroscience 8(5):955–960. https://doi.org/10.1021/acschemneuro.7b00042. PMID: 28287253.
6. Cools R, Roberts AC, Robbins TW (2008) Serotoninergic regulation of emotional and behavioural control processes. Trends in Cognitive Sciences 12(1):31–40. https://doi.org/10.1016/j.tics.2007.10.011. PMID: 18069045.
7. de Kloet ER, Vreugdenhil E, Oitzl MS, Joëls M (1998) Brain corticosteroid receptor balance in health and disease. Endocrine Reviews 19(3):269–301. https://doi.org/10.1210/edrv.19.3.0331. PMID: 9626555.
8. de Kloet ER, Joëls M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nature Reviews Neuroscience 6(6):463–475. https://doi.org/10.1038/nrn1683. PMID: 15891777.
9. Gerstner N, Krontira AC, Cruceanu C, Roeh S, Pütz B, Sauer S, et al (2022) DiffBrainNet: differential analyses add new insights into the response to glucocorticoids at the level of genes, networks and brain regions. Neurobiology of Stress 21:100496. https://doi.org/10.1016/j.ynstr.2022.100496. PMID: 36532379.
10. Goldfarb T, Kodali VK, Pujar S, Brover V, Robbertse B, Farrell CM, et al (2025) NCBI RefSeq: reference sequence standards through 25 years of curation and annotation. Nucleic Acids Research 53(D1):D243–D257. https://doi.org/10.1093/nar/gkae1038. PMID: 39526381.
11. Gray JD, Kogan JF, Marrocco J, McEwen BS (2017) Genomic and epigenomic mechanisms of glucocorticoids in the brain. Nature Reviews Endocrinology 13(11):661–673. https://doi.org/10.1038/nrendo.2017.97. PMID: 28862266.
12. Inoue T, Koyama T (1996) Effects of acute and chronic administration of high-dose corticosterone and dexamethasone on regional brain dopamine and serotonin metabolism in

rats. Progress in Neuro-Psychopharmacology & Biological Psychiatry 20(1):147–156. https://doi.org/10.1016/0278-5846(95)00299-5. PMID: 8861184.
13. Kassel O, Herrlich P (2007) Crosstalk between the glucocorticoid receptor and other transcription factors: molecular aspects. Molecular and Cellular Endocrinology 275(1–2):13–29. https://doi.org/10.1016/j.mce.2007.07.003. PMID: 17689856.
14. Laaziz A, El Mostafi H, Elhessni A, Touil T, Doumar H, Mesfioui A (2022a) Chronic clomipramine treatment reverses depressogenic-like effects of a chronic treatment with dexamethasone in rats. IBRO Neuroscience Reports 13:147–155. https://doi.org/10.1016/j.ibneur.2022.07.007. PMID: 36035970.
15. Laaziz A, El Mostafi H, Elhessni A, Azeroil F, Touil T, Boumlah S, Mesfioui A (2022b) Sex differences in behavioral, cognitive and voluntary ethanol-intake effects in dexamethasone-induced depression-like state in Wistar rat. AIMS Neuroscience 9(2):228–249. https://doi.org/10.3934/Neuroscience.2022012. PMID: 35860686.
16. Langlais D, Couture C, Balsalobre A, Drouin J (2012) The Stat3/GR interaction code: predictive value of direct/indirect DNA recruitment for transcription outcome. Molecular Cell 47(1):38–49. https://doi.org/10.1016/j.molcel.2012.04.021. PMID: 22633955.
17. Lechner J, Welte T, Doppler W (1997) Mechanism of interaction between the glucocorticoid receptor and Stat5: role of DNA-binding. Immunobiology 198(1–3):112–123. https://doi.org/10.1016/S0171-2985(97)80032-0. PMID: 9442383.
18. Malkoski SP, Dorin RI (1999) Composite glucocorticoid regulation at a functionally defined negative glucocorticoid response element of the human corticotropin-releasing hormone gene. Molecular Endocrinology 13(10):1629–1644. https://doi.org/10.1210/mend.13.10.0351. PMID: 10517666.
19. Mar JC, Kimura Y, Schroder K, Irvine KM, Hayashizaki Y, Suzuki H, Hume D, Quackenbush J (2009) Data-driven normalization strategies for high-throughput quantitative RT-PCR. BMC Bioinformatics 10:110. https://doi.org/10.1186/1471-2105-10-110. PMID: 19374774.
20. McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiological Reviews 87(3):873–904. https://doi.org/10.1152/physrev.00041.2006. PMID: 17615391.
21. Meijer OC, Buurstede JC, Schaaf MJM (2019) Corticosteroid receptors in the brain: transcriptional mechanisms for specificity and context-dependent effects. Cellular and Molecular Neurobiology 39(4):539–549. https://doi.org/10.1007/s10571-018-0625-2. PMID: 30291573.
22. Mifsud KR, Kennedy CLM, Salatino S, Sharma E, Price EM, Haque SN, et al (2021) Distinct regulation of hippocampal neuroplasticity and ciliary genes by corticosteroid receptors. Nature Communications 12(1):4737. https://doi.org/10.1038/s41467-021-24967-z. PMID: 34362910.
23. Molendijk ML, de Kloet ER (2019) Coping with the forced swim stressor: current state-of-the-art. Behavioural Brain Research 364:1–10. https://doi.org/10.1016/j.bbr.2019.02.005. PMID: 30738104.
24. Morales J, Pujar S, Loveland JE, Astashyn A, Bennett R, Berry A, et al (2022) A joint NCBI and EMBL-EBI transcript set for clinical genomics and research. Nature 604(7905):310–315. https://doi.org/10.1038/s41586-022-04558-8. PMID: 35388217.
25. Oakley RH, Cidlowski JA (2013) The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. Journal of Allergy and Clinical Immunology 132(5):1033–1044. https://doi.org/10.1016/j.jaci.2013.09.007. PMID: 24084075.
26. Paul CA, Beltz B, Berger-Sweeney J (2008) The Nissl stain: a stain for cell bodies in brain sections. CSH Protocols 2008:pdb.prot4805. https://doi.org/10.1101/pdb.prot4805. PMID: 21356903.
27. Paxinos G, Watson C (2014) The Rat Brain in Stereotaxic Coordinates, 7th edn. Academic Press.
28. Rothschild AJ, Langlais PJ, Schatzberg AF, Miller MM, Saloman MS, Lerbinger JE, Cole JO, Bird ED (1985) The effects of a single acute dose of dexamethasone on monoamine and

metabolite levels in rat brain. Life Sciences 36(26):2491–2501. https://doi.org/10.1016/0024-3205(85)90145-6. PMID: 2409422.
29. Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. Nature Reviews Neuroscience 10(3):211–223. https://doi.org/10.1038/nrn2573. PMID: 19190638.
30. Schiller BJ, Chodankar R, Watson LC, Stallcup MR, Yamamoto KR (2014) Glucocorticoid receptor binds half sites as a monomer and regulates specific target genes. Genome Biology 15:418. https://doi.org/10.1186/s13059-014-0418-y. PMID: 25085117.
31. So AYL, Chaivorapol C, Bolton EC, Li H, Yamamoto KR (2007) Determinants of cell- and gene-specific transcriptional regulation by the glucocorticoid receptor. PLoS Genetics 3(6):e94. https://doi.org/10.1371/journal.pgen.0030094. PMID: 17559307.
32. Tiutiunnik TV, Kudrinskaya VM, Obukhova DA, Vilnikova VA, Burdinskaya VO, Muruzheva Z, Karpenko MN (2025) Intraperitoneal Single Injection of Dexamethasone Leads to Region-Specific Changes in the Profile of Neuron-Specific Proteins in the Rat Brain. European Journal of Neuroscience 61(10):e70146. https://doi.org/10.1111/ejn.70146. PMID: 40415344.
33. Tiutiunnik TV, Obukhova DA, Vilnikova VA, Muruzheva ZM, Karpenko MN (2026) Single Intraperitoneal Injection of Dexamethasone Alerts Region-Specific Neurotransmitter Metabolism in Rat Brain. Neurochemical Research 51(2):98. https://doi.org/10.1007/s11064-026-04718-6. PMID: 41779097.
34. Vandesompele J, De Preter K, Pattyn F, Poppe B, Van Roy N, De Paepe A, Speleman F (2002) Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. Genome Biology 3(7):research0034.1–research0034.11. https://doi.org/10.1186/gb-2002-3-7-research0034. PMID: 12184808.
35. Zubov AS, Ivleva IS, Pestereva NS, Tiutiunnik TV, Traktirov DS, Karpenko MN (2022) Glibenclamide alters serotonin and dopamine levels in the rat striatum and hippocampus, reducing cognitive impairment. Psychopharmacology 239(9):2787–2798. https://doi.org/10.1007/s00213-022-06159-9. PMID: 35545702.

Statements and Declarations

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Competing interests

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Author contributions

Tiutiunnik TV: Methodology, Validation, Investigation, Writing—original draft.

Obukhova DA: Writing – review & editing, Investigation.

Vilnikova VA: Methodology, Writing – review & editing.

Muruzheva Z: Conceptualization.

Karpenko MN: Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

All authors read and approved the final manuscript.

The authors declare that all data were generated in-house, that no paper mill was used and that no AI tool has been used for the generation of text or figures.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

All experiments were performed in accordance with institutional guidelines and the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals as well as national laws (Ministry of Health of the Russian Federation N267, June 19, 2003; Guide for the Use of Laboratory Animals, Moscow, 2005) and permission of the Local Ethical Committee for this research Federal State Budgetary Scientific Institution “Institute of Experimental Medicine” of St. Petersburg № 2/23 from 15.06.2023.

Consent to participate: not applicable. This study did not involve human participants.

Clinical trial number: not applicable.

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