



Systematic analysis of severity in a widely used cognitive depression model for mice

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Abstract

Animal models in psychiatric research are indispensable for insights into mechanisms of behaviour and mental disorders. Distress is an important aetiological factor in psychiatric diseases, especially depression, and is often used to mimic the human condition. Modern bioethics requires balancing scientific progress with animal welfare concerns. Therefore, scientifically based severity assessment of procedures is a prerequisite for choosing the least compromising paradigm according to the 3Rs principle. Evidence-based severity assessment in psychiatric animal models is scarce, particularly in depression research. Here, we assessed severity in a cognitive depression model by analysing indicators of stress and well-being, including physiological (body weight and corticosterone metabolite concentrations) and behavioural (nesting and burrowing behaviour) parameters. Additionally, a novel approach for objective individualised severity grading was employed using clustering of voluntary wheel running (VWR) behaviour. Exposure to the paradigm evoked a transient elevation of corticosterone, but neither affected body weight, nesting or burrowing behaviour. However, the performance in VWR was impaired after recurrent stress exposure, and the individual severity level increased, indicating that this method is more sensitive in detecting compromised welfare. Interestingly, the direct comparison to a somatic, chemically induced colitis model indicates less distress in the depression model. Further objective severity assessment studies are needed to classify the severity of psychiatric animal models in order to balance validity and welfare, reduce the stress load and thus promote refinement.

Keywords

severity assessment, mice, cognitive depression, faecal corticosterone metabolites, nesting, burrowing, voluntary wheel running, animal welfare

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Animal models in psychiatry are necessary to gain insight into the molecular and cellular mechanisms of behaviour and psychiatric disorders. Since distress is a common aetiological factor in psychiatric disorders, many animal models, in particular for depression, are based on physical, environmental or social stress. This raises the ethical dilemma of balancing scientific progress with animal welfare concerns. Therefore, it is important to grade and compare severity in scientific procedures in order to be able to choose the least

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discomforting alternative while maintaining efficacy. The principle to reduce, refine and replace (the 3Rs)¹ animal experiments whenever possible has been integrated into legislation in EU Directive 2010/63 and into good scientific practice (e.g. the ARRIVE guidelines).² Within the EU, the severity of every planned procedure needs to be classified in the project authorisation process. However, the current classification of severity levels into ‘mild’, ‘moderate’ and ‘severe’ is only partly based on scientific knowledge, since systematic attempts to assess severity are scarce, particularly for psychiatric animal models.

Therefore, we performed a multimodal severity assessment study on the stress-induced cognitive depression model of learned helplessness (LH), a widely used rodent model for depression with excellent face, construct and predictive validity.³ It is based on exposure to inescapable electric foot shocks, which are classified with the highest severity score according to EU directive 2010/63. The reasons for this rating, however, are unclear; comparisons to somatic models are missing.

Hence, we analysed established parameters of impaired well-being in mice to detect the compromised welfare induced by the LH procedure, including physiological measures such as body weight loss and increased corticosterone release,^{4,5} and behavioural parameters such as nesting^{6–8} and burrowing.^{6,9} Additionally, we used the newly developed unsupervised k-means algorithm-based cluster analysis of body weight and voluntary wheel running (VWR)¹⁰ to grade the level of severity of mice receiving foot shocks individually, and we compared these results with a somatic animal model of colitis.

Material and methods

Animals and housing

Eight-week-old male C57BL/6N mice (Charles River Laboratories, Sulzfeld, Germany) were single housed in conventional macrolon cages (type II) with bedding, nesting material, tap water and food ad libitum (see Supplemental Material). The animals were pseudo-randomly assigned to the respective experimental group. Locomotion and pain thresholds were used to stratify mice into groups and to avoid confounding effects. All experiments had been approved by German animal welfare authorities (Regierungspräsidium Karlsruhe; 35-9185-81-G-199-17).

General behavioural assessment

All experiments were conducted within the first three hours of the dark phase – the active phase of the

animals – unless specified further. Locomotion was assessed using the open field test for 10 minutes in a 50 cm × 50 cm arena, and the pain threshold was assessed according to the latency to react on a hot plate (see Supplemental Material).

Mice were assigned to the following groups: (a) home cage controls (C), which remained in the colony room throughout the testing phase; (b) handling controls (H), which entered the shock boxes but never received a shock; (c) non-trained controls (N), which were exposed to avoidable foot shocks only during the shuttle box task on day 3; and (d) trained (T) mice, which received unavoidable foot shocks during the first two days of LH training and on day 3 in the shuttle box (Supplemental Table S1). In experiment 3 (see below), we omitted the non-trained controls but introduced a chemically induced colitis group (DSS) as somatic controls.¹⁰

Cognitive depression model. The LH paradigm was conducted as previously described.¹¹ Briefly, mice were transferred into chambers with stainless-steel grid floors. Trained subjects received 360 unpredictable and inescapable foot shocks (0.150 mA) on two consecutive days. On day 3, trained and non-trained control subjects were analysed for helpless behaviour in shuttle boxes. Each chamber contained a signalling light, which announced foot shocks (0.150 mA) for five seconds in one of the two compartments. The escape performance was analysed during 30 trials.

In three independent experiments, we assessed corticosterone release and typical behavioural indicators of well-being (e.g. nesting and burrowing), or we used VWR to classify severity in the different cohorts (an overview of time lines and groups in the respective experiments can be found in Supplemental Figure S1 and Table S2).

Experiment 1: faecal corticosterone metabolites

Forty-eight mice were assigned to the respective groups (see Supplemental Material). We sampled faeces to determine faecal corticosterone metabolite (FCM) concentrations before the onset (pre), during each training session (training days 1 and 2), during the shuttle box test (day 3) and one week after the LH (post LH). For each day, two samples were collected, representing (a) acute corticosterone levels during the foot shock exposure or sham treatment and (b) a delayed idle period to detect persistent effects. Samples were collected in a secondary home cage (see Supplemental Material) and were processed as described.¹² Briefly, an extract of dried and homogenised faeces was produced with

80% methanol, and an aliquot was analysed in a well-established and validated 5 α -pregnane-3 β ,11 β ,21-triol-20-one enzyme immunoassay (EIA).^{4,5}

Experiment 2: typical indicators of well-being

Twenty-eight mice were assigned to the respective groups. The nest test was performed before and three weeks after the LH procedure and the time to integrate novel material into the nest (TINT) 1 and 20 days afterwards. Burrowing was analysed 2, 8 and 21 days after the LH test.

Nest building was evaluated according to a rating scale based on cohesion and shape (see Supplemental Table S2). Additionally, we assessed the nest quality daily at 10:00 am to track this parameter throughout the experiment. In the TINT, sizzle material was introduced in the diagonally opposing corner of the nest site, and latency to integrate was measured for a maximum of 10 minutes.⁶

We placed bottles (14 cm long \times 5.5 cm \varnothing) filled with food pellets at the rear of the home cage one hour before the dark phase and observed the amount that was burrowed out of the bottle (% of total weight) after 6 and 24 hours. All mice were accustomed to the procedure one week before the LH procedure on four consecutive days.⁶

Experiment 3: VWR

Forty-eight mice were assigned to the respective groups (see Supplemental Material). VWR was recorded daily at the beginning of the dark phase. To determine the steady-state running performance, an adaptation phase of 16 days was chosen before experimental onset (see Supplemental Figure S2). The LH procedure was performed on days 2–4. Due to malfunctions in the running wheel systems and the consequential imprecision, we decided to exclude unreliable results. Two cages from each group were affected.

The colitis group received 1% dextran sulphate sodium (DSS; mol wt 36,000–50,000; MP Biomedicals, Eschwege, Germany) for five consecutive days (days 1–5) and remained in the colony room.

Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics for Windows v24 (IBM Corp., Armonk, NY). The experimental unit was the single animal. Differences were considered to be significant at $p \leq 0.05$. For more information, see Supplemental Material.

Results

FCMs reveal a short-lasting increase due to foot shocks

FCM samples as a physiological marker for stress varied significantly between different treatment groups (Figure 1). Acute FCM concentrations were elevated in trained mice on all three days of LH, while the merged handling group showed an exclusive effect on day 2 (acute: LH day 1, $H(2)=7.373$, $p=0.025$, post hoc trained vs. home cage $p=0.021$; LH day 2, $H(2)=7.373$, $p=0.025$, post hoc trained vs. home cage $p=0.001$ and merged handling vs. home cage $p=0.046$; shuttle box, $H(3)=10.291$, $p=0.016$, post hoc trained vs. home cage $p=0.016$). Overall, the FCM concentration of trained mice showed a prominent change over time in the acute sample (Friedman: $N=13$, $\chi^2(4)=13.846$, $p=0.008$) with a peak on LH day 2 and normalisation after the procedure, while FCM concentrations of home cage controls remained unchanged. The persistence of the stress response was measured in the delayed samples and became significant exclusively on LH day 2 (Figure 2; $H(2)=8.482$, $p=0.014$, post hoc trained vs. home cage $p=0.012$ and merged handling vs. home cage $p=0.066$).

Foot shocks do not affect typical well-being parameters. We analysed nesting quality, integration of nesting material, burrowing behaviour and body weight before, during and after the LH procedure (Figure 3). Repeated-measures analysis of variance did not reveal significant differences between the treatment groups or interactions over time, though some time effects became apparent for burrowing (time: $F(3, 69)=4.523$, $p=0.006$) and body weight (time: $F(4, 92)=125.561$, $p < 0.001$).

Severity evaluation using VWR behaviour-based k-means clustering does not indicate severe consequences of foot shocks. Daily body weight assessment and VWR performance were used to determine the current status of each mouse according to k-means clustering.¹⁰ Mice in the DSS group mildly but significantly lost weight compared to the other groups from day 7 onwards (Figure 4). The effect was largest on day 9 ($M=6.8\%$ ($SD=6.1\%$), $F(3, 39)=12.776$, $p < 0.001$, post hoc DSS vs. home cage $p < 0.001$, vs. handling $p < 0.001$, vs. trained $p < 0.001$). Overall, the body weight changed during the experiment (time: $F(13, 468)=33.979$, $p < 0.001$) and was influenced by DSS treatment (treatment \times time: $F(39, 468)=5.932$, $p < 0.001$; treatment: $F(3, 36)=4.930$, $p=0.006$, post hoc home cage vs. DSS $p=0.003$). Foot shocks or handling did not affect body weight.

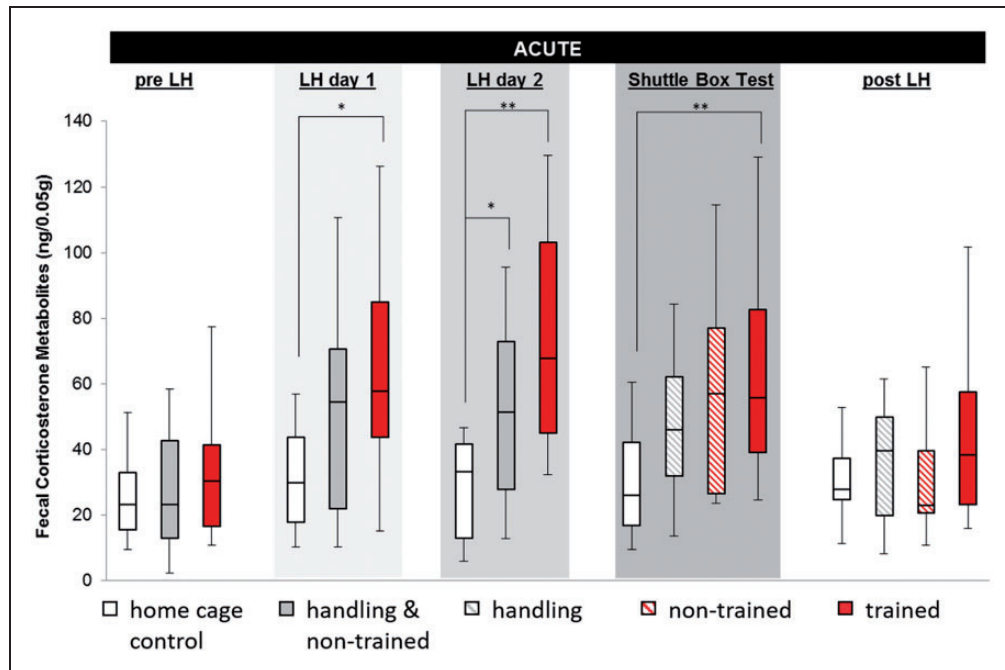


Figure 1. Concentrations of faecal corticosterone metabolites (FCMs) transiently increased after exposure to inescapable stress (trained), but also after only repetitive handling in the acute sample. Handling and non-trained were identically handled until the shuttle box test and are therefore merged until then. Data are given as boxplot diagrams showing the median (line within the box), 25% and 75% quartiles (boxes), 10% and 90% ranges (whiskers). * $p < 0.05$; ** $p < 0.01$.

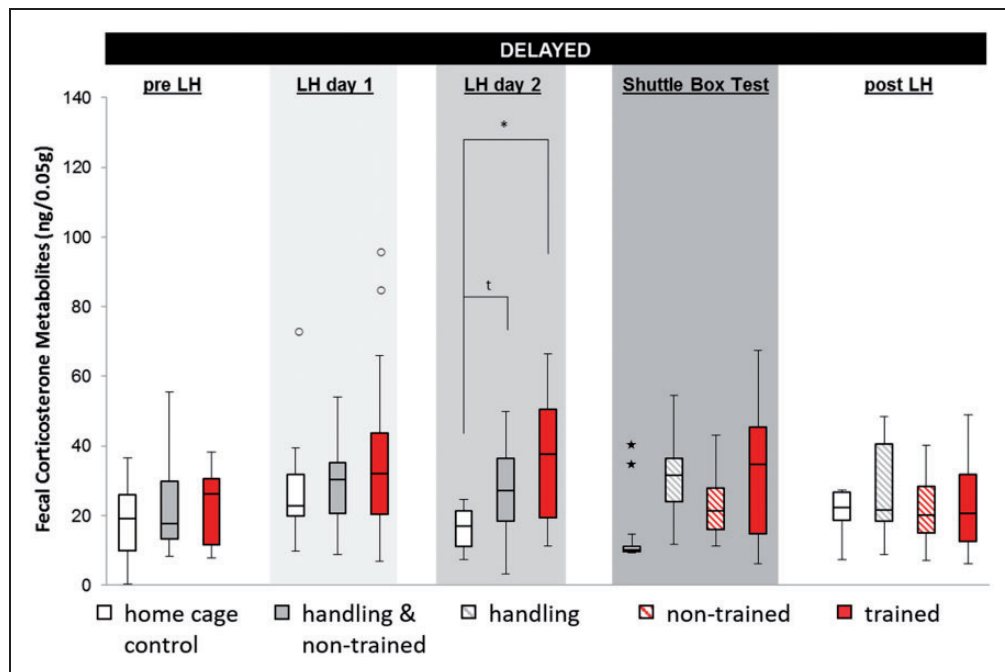


Figure 2. In the delayed sample, concentrations of FCMs were transiently increased after repetitive exposure to inescapable stress, while handling and escapable shock did not cause any effects. Handling and non-trained animals were identically handled until the shuttle box test and are therefore merged until then. Data are given as boxplot diagrams showing the median (line within the box), 25% and 75% quartiles (boxes), 10% and 90% ranges (whiskers) and outliers (dots (1.5- to 3-fold interquartile range) or star (>threefold interquartile range)). ^t $p = 0.06$; * $p < 0.05$.

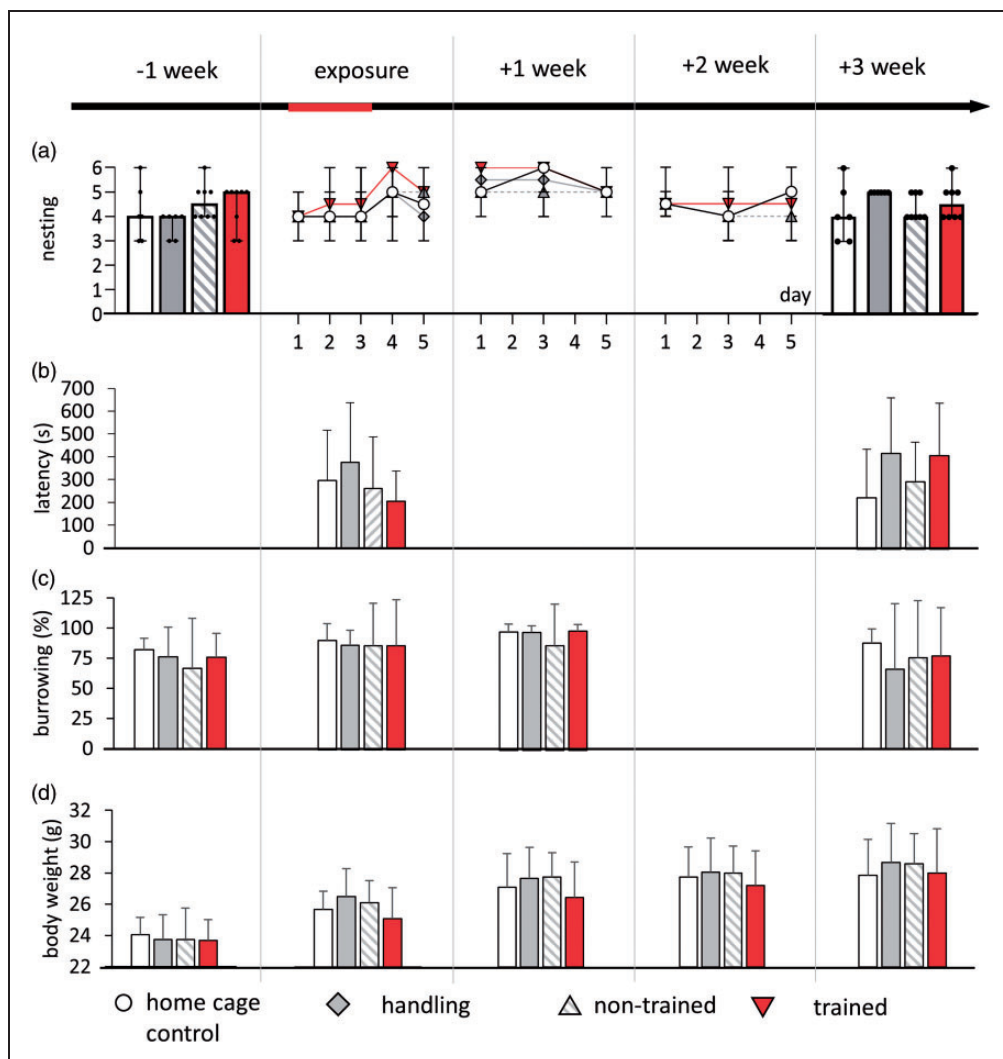


Figure 3. Exposure to shocks did not alter behavioural parameters or body weight. Days of shocks are indicated in red on the time line. (a) Neither the nest tests one week before stress and three weeks after nor daily nesting scores during exposure revealed differences. (b) The time to integrate material into the nest (TINT) was similar in all treatment groups, as well as (c) burrowing. (e) Body weight was not affected. In (a), graphs represent the median and 95% confidence interval (CI). In (b)–(d), graphs represent the mean \pm standard deviation (SD).

VWR behaviour was sensitive to both the foot shock exposure and DSS treatment (Figure 5). During the three days of the LH procedure, the performance changed (time: $F(2, 70) = 8.842$, $p < 0.001$), and a general treatment effect was observed (treatment: $F(3, 35) = 5.367$, $p = 0.004$). The trained group differed significantly from the home cage ($p = 0.008$) and DSS ($p = 0.014$) group but not from the handling controls. However, the DSS effects were more distinct, with a mean reduction of 40.7% ($SD = 23.1\%$) on day 8 compared to a mean of 64.0% ($SD = 9.8\%$) following foot shocks on day 4. The DSS-induced reduction was significant throughout the procedure

(time: $F(13, 455) = 21.475$, $p < 0.001$; treatment \times time: $F(39, 455) = 6.232$, $p < 0.001$; treatment: $F(3, 35) = 4.310$, $p = 0.011$). In the pairwise comparison, a significant difference was only detected between the home cage and the DSS group ($p = 0.008$).

The severity score determined by the k-means cluster analysis revealed that the majority of subjects only displayed a level 0 or level 1 severity during the three days of the LH procedure (Figure 6). Only 1/12 trained mice reached severity level 2 after each training session. On the other hand, the DSS treatment led into a shift to level 2 severity for up to 8/10 mice (day 8). Most mice recovered by day 12.

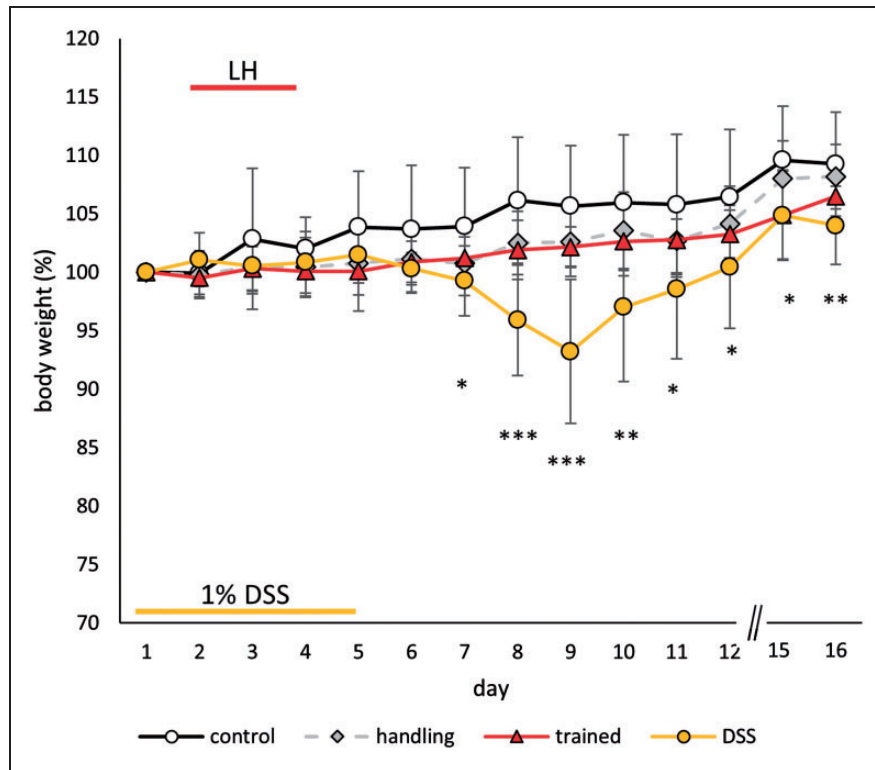


Figure 4. Body weight development (% change from baseline) during and after the respective treatments. Data are given as the mean \pm SD.

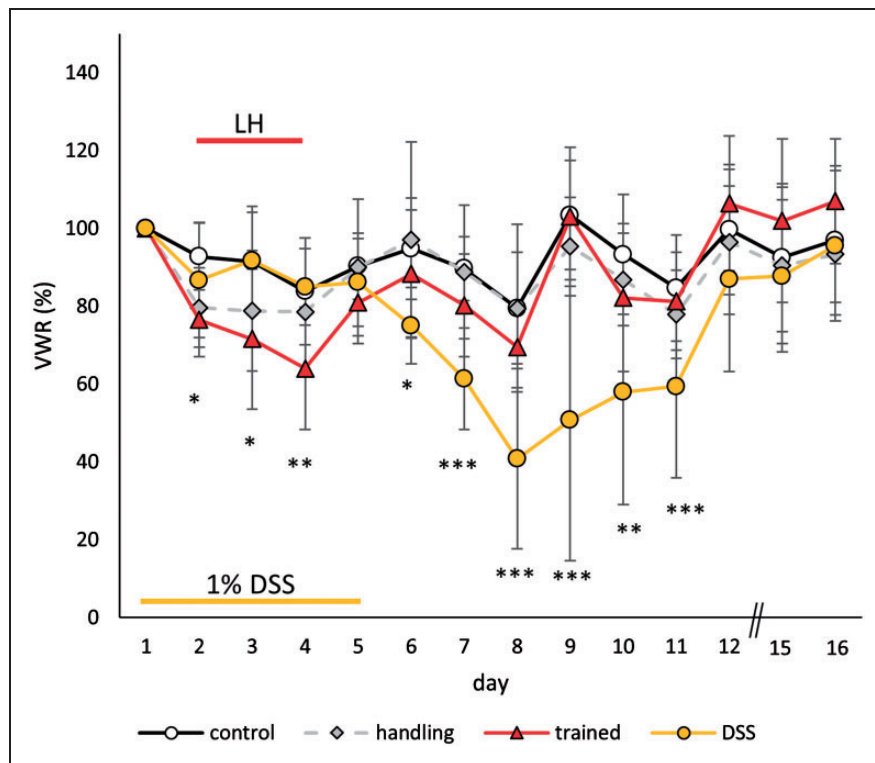


Figure 5. Voluntary running development (% change from baseline) during and after the respective treatments. Data are given as the mean \pm SD.

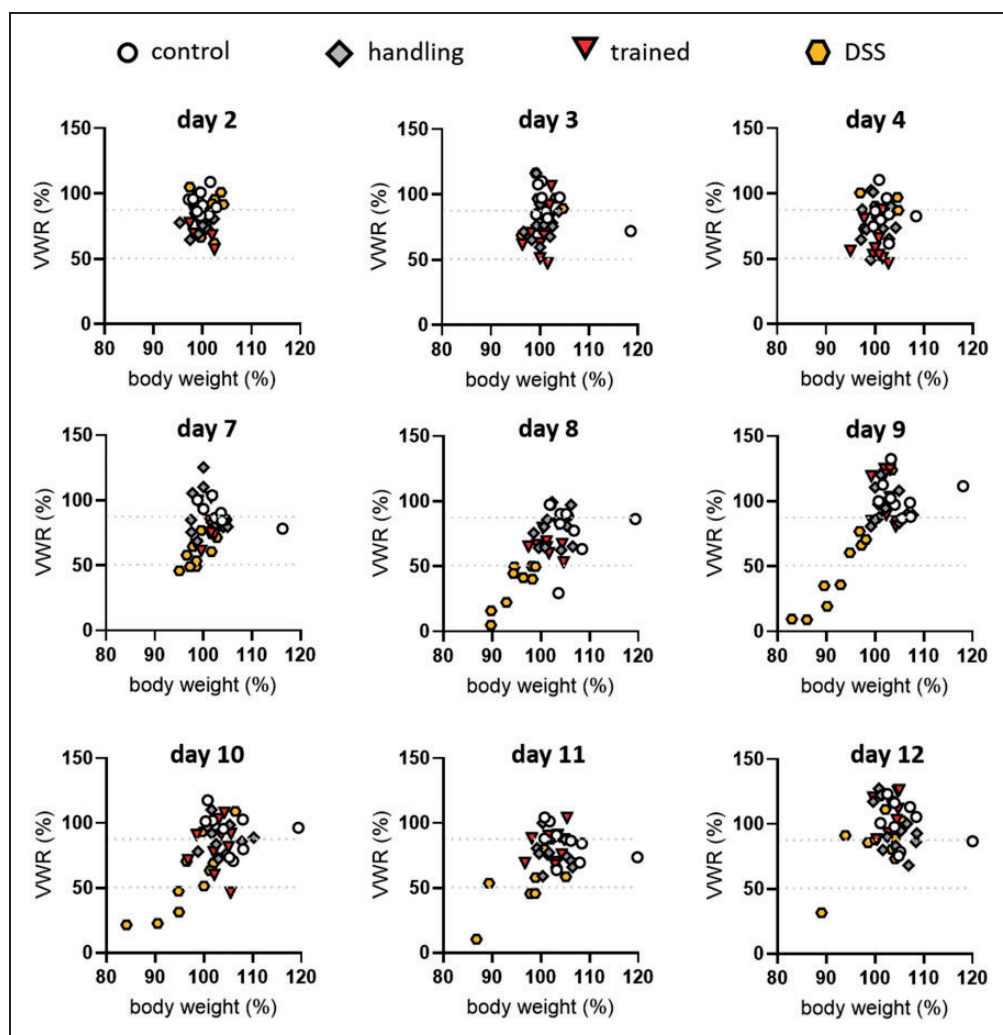


Figure 6. Voluntary wheel running plotted against body weight in k-means cluster analysis with cluster borders (dashed lines) at different dates of the experiment. Cluster borders separate regions of the graphs into severity level 0 (>87.37), level 1 (between 50.16 and 87.37) and level 2 (<50.16).

Discussion

The objective of this study was to perform an evidence-based evaluation of severity in the LH cognitive depression model. For that purpose, we used an established battery of physiological and behavioural tests to detect the magnitude of evoked stress and discomfort.

Our results demonstrate a significant increase in FCMs in the acute samples after exposure to escapable and inescapable shocks, but also a comparable elevation of FCM concentrations in non-shocked handling controls. Apparently, it was not only the foot shocks that triggered the stress response. Other influencing factors might be the transport to the experimental room, or potentially even more bearing, the introduction to the chambers per se. The chamber includes a metal grid floor, no bedding material and no possibility to build a nest, eat or drink. Although the animals are not

physically restrained in the chambers and there is no illumination, we consider the chamber to be a stressful environment compared to a home cage setting. The surroundings somewhat resemble metabolic cages. The 2010/63/EU directive categorises short-term (<24 hours) exposure to metabolic cages as mild in severity. On day 2, repeated exposure to the stressful condition could have triggered a profound stress response due to the previously established association.

However, only the recurrent exposure to inescapable shocks led to a significant increase in the delayed samples. FCMs have been found to be a sensitive parameter of adrenocortical activity,¹³ and the lack of LH-induced effects might reflect that there was no difference in the magnitude of the acute stress response and that the treatments could be considered equal in this respect. However, caution is advised, as not every type of stressor may be reflected in measured glucocorticoids.^{14,15}

Therefore, several physiological and behavioural parameters (i.e. nesting, burrowing or body weight) are typically measured to evaluate if well-being is compromised in stressed animals. Yet, none of the above-mentioned parameters was altered by avoidable or unavoidable foot shocks, although this procedure is typically considered a potent stressor and expected to induce key depressive-like behavioural features. Only when analysing VWR performance was a change in the trained group visible. Analysing this parameter on an individual level, two individuals reached severity level 2 according to the k-means cluster analysis during the LH procedure, although their body weight remained unaffected. Thus, the VWR-based assessment was more sensitive to compromised welfare than typical home cage observations.

Experiment 3 was designed to uncover and grade the impact of the LH model compared to the DSS-induced mild colitis model using the unbiased individual severity grading by k-means cluster analysis.¹⁰ We chose the colitis model because this method was initially implemented in this model and allowed a direct comparison by replicating the previous study. Additionally, it offers a thoroughly described and evidence-based severity assessment^{8,10,16} and an approved severity classification according to the 2010/63/EU directive dependent on the doses and duration of the treatment. Here, we decided to use the moderate severity because it was sufficient to induce detectable impairments in the wheel running analysis and hence serves as a suitable positive control, although the inflicted pain is of a different modality in the respective models. While the pain is temporarily limited in the depression model, it is chronic in colitis. This might affect the running outcome, which could be a reason for the stronger impairment in colitis. The psychological load of depression could in general contribute less to the running performance than pain does. Further studies on running in mice with different emotional states would be necessary to clarify this question.

Here, we observed a larger fraction of subjects in severity level 2 in the colitis model compared to the LH depression model. The foot shock-induced effects rather resembled the milder effects of facial vein phlebotomy.¹⁰ Hence, colitis comprises the highest strain and stress, while this LH protocol and blood sampling similarly comprise low levels of distress induction.

Assessing severity requires detailed consideration of potential stressors, which operate as confounding factors. Ideally, the stressed group of interest would be compared to a non-stressed control group. Avoiding stress in animal maintenance and handling is very challenging, especially in an experimental context. Circumstantial parameters (e.g. housing conditions)

can be associated with a stress response or even impairments of well-being.¹⁷ Single housing is often considered harmful to mice.¹⁸ Yet, we decided to house our mice individually, since in our set-up male mice showed less burden.¹¹ Other factors needed to be taken into account. To ensure that the result of the LH was not confounded by altered pain threshold or locomotor differences, we needed to perform the respective experiments first. The brief exposure to a painful stimulus and the illumination during the dark phase in the tests can induce stress. Consequently, a ceiling effect might mask the differences between the treatment groups. We tried to avoid this by temporal separation of the previous test to the LH paradigm.

According to EU directive 2010/63, exposure to an inescapable electric shock is considered severe, while DSS-induced colitis is classified as mild to moderate at the dose applied here, and facial-vein phlebotomy is classified as mild. This constitutes a dilemma, since the evidence from the cluster analysis showed bigger fractions of DSS-treated mice with a level 2 burden than those subject to LH treatment. In relation, foot-shocked mice were less affected. An absolute assessment is, however, more difficult. Assuming that level 2 is equal to moderate severity, the fact that most shocked mice remained at level 1 during the LH procedure, which could be considered mild, indicates the mismatch of the current legal regulations, which are rather supported by anthropomorphic concepts than evidence-based severity. Therefore, more comparative studies are needed to assess and classify the severity of the LH model and other psychiatric animal models objectively.

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Supplemental material

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Résumé

Les modèles animaux sont indispensables à la recherche psychiatrique pour comprendre les mécanismes de comportement et les troubles mentaux. La détresse est un facteur étiologique important des maladies psychiatriques, notamment la dépression, et est souvent utilisée pour imiter la condition humaine. Les considérations modernes de bioéthique nécessitent un équilibre entre les progrès scientifiques et le bien-être des animaux. Par conséquent, une évaluation de la gravité des procédures scientifiquement fondée constitue une condition préalable au choix du paradigme le moins compromettant selon le principe des 3R. L'évaluation de la gravité des troubles psychiatriques dans les modèles animaux est rare, en particulier dans la recherche menée sur la dépression. Nous avons évalué ici la gravité dans un modèle cognitif de la dépression par l'analyse des indicateurs de stress et de bien-être, dont les indicateurs physiologiques (poids corporel et concentrations de métabolites de corticostérone) et comportementaux (nidification et comportement fouisseur). En outre, une nouvelle approche du classement objectif et individualisé de la gravité était utilisée employée en regroupant les comportements d'activité dans une roue d'exercice volontaire (VWR). L'exposition au paradigme évoquait une élévation transitoire de la corticostérone, mais n'affectait ni le poids corporel, ni la nidification ou le comportement fouisseur. Cependant, la performance de VWR était affectée après exposition à un stress récurrent et le niveau de gravité individuel augmentait, ce qui indique que cette méthode est plus sensible pour détecter un bien-être compromis. Fait intéressant, la comparaison directe avec un modèle de colite somatique induit chimiquement indique moins de détresse dans le modèle de la dépression. D'autres études d'évaluation objective de la gravité sont nécessaires pour classer la gravité des

modèles animaux de troubles psychiatriques, afin d'équilibrer la validité et le bien-être, de réduire le niveau de stress et de promouvoir ainsi l'amélioration.

Abstract

Tiermodelle in der psychiatrischen Forschung sind unverzichtbar für die Erforschung von Verhaltensmechanismen und psychischen Störungen. Belastung und Stress ist ein wichtiger ätiologischer Faktor bei psychiatrischen Erkrankungen, insbesondere bei Depressionen, und wird oft zur Nachahmung des menschlichen Zustandes eingesetzt. Die moderne Bioethik fordert ein ausgewogenes Verhältnis zwischen wissenschaftlichem Fortschritt und Tierschutzbelangen. Daher ist eine wissenschaftlich fundierte Schweregradbeurteilung der Verfahren Voraussetzung für die Wahl des am wenigsten beeinträchtigenden Paradigmas nach dem 3 R-Prinzip. Evidenzbasierte Schweregradbeurteilung in psychiatrischen Tiermodellen gibt es selten, insbesondere in der Depressionsforschung. In der vorliegenden Studie bewerteten wir Schweregrade in einem kognitiven Depressionsmodell, indem wir Indikatoren für Stress und Wohlbefinden analysierten, darunter physiologische (Körpergewicht und Kortikosteron-Metaboliten-Konzentrationen) und verhaltensbedingte (Nestbau- und Wühlverhalten). Darüber hinaus wurde ein neuartiger Ansatz für die objektive individualisierte Schweregradklassifizierung unter Verwendung von Clustering von freiwilliger Laufradaktivität (VWR) eingesetzt. Die Exposition gegenüber dem Modell evozierte eine vorübergehende Kortikosteronerhöhung, beeinflusste aber weder das Körpergewicht noch das Nestbau- oder Wühlverhalten. Allerdings war die VWR-Leistung nach wiederholter Stressbelastung beeinträchtigt und der individuelle Belastungsgrad erhöht, was darauf hindeutet, dass mit dieser Methode beeinträchtigtes Wohlergehen besser erkannt werden kann. Interessanterweise deutet der direkte Vergleich mit einem somatischen, chemisch induzierten Kolitis-Modell auf eine geringere Belastung im Depressionsmodell hin. Weitere objektive Studien zur Schweregradbewertung sind erforderlich, um die Belastung psychiatrischer Tiermodelle zu klassifizieren, um wissenschaftliche Validität und Tierschutz in Einklang zu bringen, die Stressbelastung zu reduzieren und so Verbesserungen zu fördern.

Resumen

Los modelos animales usados en la investigación psiquiátrica son indispensables para conocer la mecánica de la conducta y los trastornos mentales. La ansiedad es un importante factor etiológico en las enfermedades psiquiátricas, especialmente en la depresión, y suele utilizarse para imitar la condición humana. La bioética moderna exige el equilibrio entre el progreso científico y las inquietudes sobre el bienestar de los animales. Es por ello que la evaluación de la intensidad de los procedimientos con base científica es uno de los requisitos previos a la hora de elegir el paradigma menos peligroso según el principio de las 3R. Existen escasas evaluaciones de la intensidad con base en pruebas sobre modelos de animales psiquiátricos, principalmente por lo que respecta a la investigación sobre la depresión. En este caso, evaluamos la intensidad en un modelo de depresión cognitiva mediante el análisis de indicadores de estrés y bienestar, como de tipo fisiológico (peso corporal y concentración de metabolitos de corticosterona) y de tipo conductual (conducta en la nidificación y las madrigueras). Igualmente, se adoptó un enfoque innovador para la clasificación de la intensidad individualizada objetiva usando un agrupamiento de conductas de carrera voluntaria en rueda (en inglés, VWR). La exposición al paradigma apuntó a una subida transitoria de la corticosterona, pero no afectó el peso corporal ni la conducta en la nidificación o las madrigueras. No obstante, el rendimiento en la VWR se vio alterado tras una exposición recurrente al estrés, y el nivel individual de intensidad aumentó, lo que indica que este método es más sensible a la detección del bienestar en peligro. Un dato interesante es que la comparación directa con el modelo de colitis inducido químicamente y somático demuestra menos ansiedad en el modelo de depresión. Son necesarios nuevos estudios sobre la evaluación de la intensidad objetiva con los que se clasifique la intensidad de modelos animales psiquiátricos con el fin de equilibrar la validez y el bienestar, y reducir la carga de estrés, de forma que se promuevan unos métodos más sofisticados.