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Severity assessment from an animal's point of view

Belastungsbeurteilung aus Sicht des Tieres

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Abstract

Severity assessment in animal experimentation is a complex biomedical and ethical issue. While the requirements for laboratory animal science regarding assessment of severity are getting more demanding, criteria for such an assessment are still biased by uncertainty. The interpretation of physiological and behavioral measures in relation to animal welfare is difficult and often reflecting an educated gut feeling rather than scientifically sound conclusions. Here, we argue for the importance of including the animals' perspective into severity assessment. Preference tests are a straightforward approach in asking the appraisal of different goods. However, preference for one good over another does not necessarily indicate suffering if the access to the preferred good is denied. Nor can the overall severity of an experimental measurement be derived solely from the fact that the animal would rather not participate in such a procedure. To gain a better understanding of the valence of choices made, there is demand for sophisticated tests which allow estimating the strength of the respective preferences. Animals usually cannot choose to avoid experimental procedures and such experiences leave traces in internal affective states. These emotion-like states can be revealed using tests of cognitive bias, which ask the animal if future expectations are "optimistic" or "pessimistic". Advancing these methods on testing cognitive bias in mice allows a comprehensive severity assessment taking internal affective states into account. The set of measures proposed here include the animal's point of view in severity assessment with regard to their preference and valence of future expectations.

Keywords: choice test, preference test, cognitive bias, refinement, animal welfare

Zusammenfassung

Die Beurteilung der Belastung im Tierversuch stellt eine komplexe ethische und biomedizinische Herausforderung dar. Die Anforderungen an die Versuchstierkunde bezüglich der Belastungseinschätzung steigen stetig. Derzeit fehlen jedoch wissenschaftliche überprüfbare Messparameter um die Belastungen aus Sicht der Tiere einschätzen zu können. Die Interpretation von Verhaltensdaten und physiologischer Parameter im Zusammenhang mit tierlichem Wohlergehen ist nicht immer eindeutig; anstelle valider wissenschaftlicher Kriterien tritt mitunter ein „Bauchgefühl" des Beurteilenden. Dieser Übersichtsartikel diskutiert die besondere Bedeutung, die Tiere selbst bei Belastungseinschätzung zu „befragen". In Wahlversuchen können die Tiere zwischen verschiedenen Ressourcen wählen. Die Bevorzugung eines Gutes gegenüber einem anderen führt dann aber nicht zwangsläufig zu Leid, wenn das Tier keinen Zugang zum präferierten Gut hat. Um die Präferenzen der Tiere besser beurteilen zu können, besteht ein dringender Bedarf für aussagekräftigere Präferenztests. Ferner können Tiere üblicherweise nicht frei entscheiden, ob sie an bestimmten Versuchen teilnehmen wollen. In Tierversuchen getestet zu werden, könnte den emotionalen Status der Tiere messbar beeinträchtigen. Zwar sind die inneren emotionalen Zustände nicht immer offensichtlich, sie können jedoch mit Hilfe des Erwartungsvalenztests experimentell sichtbar gemacht werden. Dieses Verfahren gibt Aufschluss über die Erwartungshaltung der Tiere gegenüber zukünftigen Ereignissen, anthropomorph formuliert, ob sie die Zukunft eher „optimistisch" oder „pessimistisch" sehen. Eine Erweiterung dieses Erwartungsvalenztests für Mäuse könnte eine umfassendere Belastungseinschätzung möglich machen, die auch die emotionalen Zustände der Tiere berücksichtigt. Die hier vorgeschlagenen Methoden zielen auf eine Belastungseinschätzung aus Sicht der Tiere ab, indem deren Präferenz und Erwartungsvalenz mit einbezogen werden.

Schlüsselwörter: Präferenztest, Wahlversuch, Erwartungsvalenz, Refinement, Wohlergehen

Introduction

Suffering is an internal mental state which is experienced by an individual and thus cannot be measured directly. In assessing the mental state of others we largely rely on the argument-by-analogy: If we observe a reaction that typically would be related to a distinct mental state in ourselves, we believe that the observed subject is in a comparable mental state. The same line of argument applies for physiological measures as well as for behavioral signs. For example, in a recent paper (Karabeg et al. 2013) the stress-physiological consequences of testing a knockout mouse model in two spatial tasks for learning and memory were analyzed. In the classical water maze task (Morris 1984) a mouse is put into a pool of water and has to find a submerged platform. Similar spatial skills can be tested without forcing mice to swim using a Barnes maze, a circular platform with 12 holes close to the edge of the platform. Only one of the 12 holes leads to a tube which is connected to the home cage of the animal while the other holes are dead ends. Both tests are routinely performed worldwide in behavioral phenotyping to assess spatial learning and memory formation. While generally speaking, both tests seem to be equally suitable, they emphasize on slightly different aspects of learning and memory. Therefore sometimes procedures are selected depending on species (e.g., Frick et al. 2000, Stranahan 2011, Whishaw and Tomie 1996), strain (e.g., Holmes et al. 2002), experimental design, and scientific objective (e.g., Inman-Wood et al. 2000). However, experience with local authorities for approval of animal experimentation revealed that the water maze was classified as much more severe. This classification was largely based on the argument-by-analogy, representing the anthropomorphic view of how it would feel to be thrown in a pool of water. Admittedly, this classification might indeed be correct, but scientifically it is not at all well-founded. In both tests a significant increase in glucocorticoid stress hormones (GC) could be shown. Above being perceived as stressful it is vastly unknown how severe the procedures are experienced by the mice themselves. For example, being confronted with an inescapable situation like being forced to swim, leads to panic-like symptoms which is accompanied by stress and a number of immediate early reactions in the amygdala (Hohoff et al. 2013). However, once the mice have learned that the water maze is escapable, they might evaluate the procedure differently.

Moreover, animals do not necessarily show obvious behavioral signs of suffering within a wide range of discomfort. This is especially true for species such as mice that are preyed upon. Vice versa, physiological signs related to stress do not necessarily indicate bad welfare. For example, GC are not related to the valence of arousal (they increase during mating as well as in fear of death) and thus stress in itself is not necessarily a sign for bad welfare (Dawkins 2011, Korte et al. 2007). Above the common measurements utilized for severity assessment of behavioral, physiological, and clinical measures (see Keubler et al. 2018) experiments asking the animals to rate the current state are therefore of utmost importance. Although animals do not fill in questionnaires, they can be "asked" using preference tests and tests on emotional valence (Dawkins 2011, Kloke et al. 2014). We will outline the different approaches that seem to be feasible for severity assessment from an animal's point of view. To simplify matters, we will focus on mice as this is the model species which is most commonly used in animal experimentation (in 2016 66% of all tested animals in Germany were mice).

Preference tests

There are three typical designs used in preference testing: the T-maze, the home cage based preference test and conditioned place preference (or place aversion, respectively). In all three designs, the animal gets to choose between two options. The option chosen more often is then said to be preferred or, at least, less avoided. For an overview of preference tests conducted with mice see Table 1.

T-maze

In a simple design, preference can be tested in T- (or Y-) mazes by giving a binary choice between either of two arms (Figure 1). Such measures are sufficient to rate certain goods against each other. For example, if given the choice, mice usually prefer almond flakes over oat flakes or plain water over salted water (Novak et al. 2016). Also, even fruit flies (*Drosophila melanogaster*) can perform T-maze tests (Fujita and Tanimura 2011).

Using a T-maze, preference can be measured in discrete or continuous trials. For discrete measurement, within each trial the animal is required to make a definite choice, e.g., left or right (Patterson-Kane et al. 2001, Pioli et al. 2014, Ras et al. 2002). For continuous measurement, the animal stays in the T-maze for a defined period of time. Here, preference is ascertained by the time the animal spends in one arm or the other. However, if one wants to extend the testing period to a full day time or longer, instead of T-maze preference tests, home cage based preference tests are more suitable. Moreover, T-maze preference tests often have the disadvantage that they involve handling, placing the animal in an uncomfortable test apparatus, and also might not match the

TABLE 1: *Conducted preference tests investigating the welfare of mice, sorted by the main topic and test. "Number of compartments" focuses on the setup of the used apparatus, "strength assessed" provides information on whether additional obstacles were introduced to measure the strength of preference. Shown references are based on the search terms "preference AND mice[MeSH]" in pubMed, access on 05.01.2018.*

category	comparison of	method	number of compartments	duration (test)	strength assessed	reference
bedding	paper bedding material	home cage based preference test	4 + center	48 h habituation + 12 h of testing	no	Ago et al. 2002
	bedding color		(2 + center) or (3 + center)	24 h habituation + 24 h testing		Kawakami et al. 2012
	particle size of softwood bedding		2	1 week		Kirchner et al. 2012
	amount of cage bedding					Freymann et al. 2015
	amount of cage bedding					Freymann et al. 2017
	bedding material	T-maze	2 + center	30 min	no	Moehring et al. 2016
bedding, cage property	wire cage floor, bedding material, partical size of bedding	home cage based preference test	(2 + center) or (4 + center)	48 h	no	Blom et al. 1996
bedding and enrichment	bedding and nesting material	home cage based preference test	4 + center	24 h	no	Kawakami et al. 2007
enrichment	nesting material	home cage based preference test	4 + center	48 h	no	Van de Weerd et al. 1997
	running wheels		1	10 days		Banjanin and Mrosovsky 2000
	nest boxes		2 or (4 + center)	48 h or 24 h		Van Loo et al. 2005
	houses		1	12 h		Soerensen et al. 2009
	empty cage vs. locomotion loop, running wheel and tunnel system		4	3 days	lever presses	Sherwin 1998
	standard cage vs. enriched cage (climbing material)		2	24 h		Lewejohann and Sachser 2000
enrichment, cage property	nesting material, nest boxes, wire cage floor	home cage based preference test	2 + center	48 h	wire floor	Van de Weerd et al. 1998
enrichment, social contact	social contact vs. standard cage, social contact vs. enriched cage (nesting material)	home cage based preference test	2 + center	48 h	no	Van Loo et al. 2004
	cage with or without companions vs. empty cage and cage with or without companions vs. cage with enrichment (running wheel)		2	3x 24 h (alternating with or without companions)	lever presses	Sherwin 2003
	enriched cage with companions vs. empty cage		2	24 h or 6 days	lever presses	Sherwin 2007
	enriched cage with companion vs. empty cage		3 or 4	> 3 days	water basin	Lewejohann et al. 2010
social contact	sexual partners (males vs. ovariectomized females, with or without mutated androgen receptor)	Y-maze	2 + center	10 min	no	Bodo and Rissman 2007
	sexual partners (with or without dihydrotestosterone after birth)		2 + center	20 min		Bodo and Rissman 2008
	anesthetized male vs. anesthetized ovariectomized female, anesthetized ovariectomized female vs. anesthetized ovariectomized female with oestradiol	T-maze	2 + center	10 min	no	Wersinger and Rissman 2000
	dominant vs. subordinate cage companion (with or without pain)		2 + center	5 min habituation + 15 min testing		Watanabe 2014
	sexual partner (estrous female vs. male, with or without Semaphorin 7A)		2 + center	15 min		Schellino et al. 2016
	empty cage vs. inhabited cage (with familiar subordinate companion, familiar dominant companion or unfamiliar companion)	home cage based preference test	2 + center	24 h	no	Van Loo et al. 2001
	restrained companion vs. empty area, free moving companion vs. empty area, restrained companion vs. free moving companion, free moving companion vs. free moving companion in pain	T-maze, conditioned place preference test	2 + center	5 min habituation + 15 min testing	no	Watanabe 2012
	sexual partners (intact male vs. estrous female, estrous female vs. long-term ovx female, intact male vs. long-term gdx male)	conditioned place preference	2 + center	9 min	no	Brock and Bakker 2011

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category	comparison of	method	number of compartments	duration (test)	strength assessed	reference
social contact, genetics	sexual partner from same or different strain	Y-maze	2 + center	< 30 min	no	Yanai and McClearn 1972
	sexual partner from same or different strain					Yanai and McClearn 1973a
	sexual partner from same or different strain (with foster parents from different or same strain)					Yanai and McClearn 1973b
	sexual partners with different genetic backgrounds (MHC)	T-maze	2 + center	4 h or 12 h	no	Eklund 1997
	bedding from sexual partners with different genetic backgrounds, sexual partners with different genetic backgrounds (MHC)			15 min or 4 h or 12 h		Eklund 1998
	sexual partner from same or different strain (across the estrous cycle)			1 h or 15 min		Zinck and Lima 2013
	sexual partners from different populations (wild mice)		4 + center	5,5 days		Linnenbrink and von Merten 2017
social contact, odor	female vs. preputialectomized female, bedding from males vs. bedding from preputialectomized males	T-maze	2 + center	5 min	no	Hayashi 1979
	female or male vs. empty arm, odor from estrous female vs. odor from male, bedding from estrous female vs. bedding from male	Y-maze	2 + center	5 min		Bakker et al. 2002
	urine from sexual partners of different subspecies (wild mice)			10 min		Ganem et al. 2008
	urine from sexual partners of different populations (wild mice)			5 min		Latour et al. 2014
	anesthetized anestrous female vs. anesthetized estrous female, bedding from estrous female vs. clean bedding (with or without aromatase enzyme)	conditioned place preference	2 + center	30 min		Pierman et al. 2006
social contact, noise	intact vs. devocalized males	T-maze	2	3 min	no	Pomerantz et al. 1983
social contact, pharmaceutics	social contact (morphine- or saline-paired, with or without amygdala lesion)	conditioned place preference	2	15 min	no	Borlongan and Watanbe 1994
	social contact with and without oxytocin		2 + center	10 min		Kent et al. 2013
	social contact with and without ethanol		1			Wood and Rice 2013
	social contact with and without ethanol					Kent et al. 2014
	social contact with and without ethanol (with or without oxytocin or vasopressin receptors)					Wood et al. 2015
pharmoceutics/ welfare	morphine vs. saline (used to assess welfare)	conditioned place preference	2 + center	15 min	no	Roughan et al. 2014
nutrition	corn oil vs. water, linoleic acid vs. water	conditioned place preference	2 + center	30 min	no	Takeda et al. 2001
nutrition	standard diet vs. fat standard diet or sucrose diet (with or without restricted food, with or without nociceptin)	conditioned place preference, operant chamber preference test	2 or 1	20 min or 1 h	no or lever presses	Koizumi et al. 2009
cage property	cage color	home cage based preference test	4 + center	24 h habituation + 4 days testing	no	Sherwin and Glen 2003
cage property, enrichment	air exchange rate of indiviually ventilited cages, nesting material		2	1.5 days to 12 days		Baumans et al. 2002
cage property, social contact	cage with companion vs. empty cages of 3 different sizes		2	24 h	lever presses	Sherwin 2004
odor	cage-change interval	home cage based preference test	4 + center	48 h	no	Godbey et al. 2011
	biological mother and another unfamiliar lactating female (pubs with or without olfactory marker protein)		1	10 min		Lee et al. 2011
	bedding from estrous or non-estrous females, clean bedding (with or without an allylic neurosteroid)	Y-maze	2 + center	5 min		Kavaliers et al. 1994
	male urine of two different strains across estrous cycle			10 min		Yano et al. 2012
	no stress, post- or after-stress urine from same or different strain	similar to T-maze	2 + center	30 s		Surinov and Zhovtun 2010
	clean vs. used bedding material	conditioned place preference	2 + center	10 min		Fitchett et al. 2006

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category	comparison of	method	number of compartments	duration (test)	strength assessed	reference
odor, nutrition	milk chocolate vs. standard diet, odor of milk chocolate vs. no odor	conditioned place preference	2 + center	15 min	no	La Mela et al. 2010
noise	music vs. silence	similar to T-maze	2 + center	3 h	no	Yang et al. 2012
	male mice ultrasonic vocalization (with male- or female-soiled bedding or a pheromone)	T-maze	2 + center	5 min		Asaba et al. 2014
	ultrasonic vocalization of mice			10 min		Asaba et al. 2015
noise, genetics	male ultrasonic vocalization vs. silence, male ultrasonic vocalization from different populations and species	T-maze	2 + center	310 s	no	Musolf et al. 2015
visual patterns	paintings, with or without morphine	conditioned place preference	2 + center	15 min	no	Watanabe 2013
	videos of conspecifics social behaviors, with or without morphine		?	?		Watanabe et al. 2016
temperature	cage temperature (without nesting material)	home cage based preference test	3	3 days	no	Gaskill et al. 2009
	cage temperature with or without gonads		2	4 days		Kaikaew et al. 2017
temperature, enrichment	cage temperatur with or without nesting material	home cage based preference test	3	3 days	no	Gaskill et al. 2011
	enriched cage (different amounts of nesting material) vs. empty cage with same or higher temperature		2	24 h		Gaskill et al. 2012
stress	predictable vs. Unpredictable footshocks	conditioned place preference	2	15 min	no	Orsini et al. 2002
-	validation of the home cage based preference test	home cage based preference test	4 + center	48 h	no	Blom et al. 1992
-	validation of the home cage based preference test		2	12 h to 30 h		Tsai et al. 2012
examples for pharmaceutics and conditioned place preference						
pharmaceutics	nikotine	conditioned place preference	2	15 min	no	Ise 2014
	cocaine			30 min		Hilderbrand and Lasek 2014
	morphine			30 min		Koek, 2016
temperature, pharmaceutics	temperature, ethanol	conditioned place preference	2	60 min	no	Dickinson and Cunningham 1998
examples for two bottle tests (home cage based preference test)						
nutrition	fat and sugar flavor	home cage based preference test (two bottle test)	1	48 h to 4 days	no	Sclafani 2007
	high-fat diet vs. regular diet			5 days		Buttigieg et al. 2014
	fat emulsion vs. sucrose solution			10 min		Sakamoto et al. 2015
nutrition/ pharmaceutics	saccharin, cocain-paired saccharin	home cage based preference test (two bottle test)	1	1 h	no	Freet et al. 2013
examples for operant chamber preference tests						
nutrition	stimuli correlated with food under high deprivation conditions vs. stimuli correlated with food under low deprivation conditions	operant chamber preference test	1	5 min	nose pokes	Lewon and Hayes 2015
social contact, nutrition	validation of operant social motivation paradigms (social companion vs. liquid food)	operant chamber preference test	2	60 min	lever presses	Martin et al. 2014
social contact, nutrition	social companion vs. liquid food	operant chamber preference test	2	60 min	lever presses	Martin and Iceberg 2015
nutrition, time	small amount of pellets with short delay vs. Greater amount of pellets with longer delay	operant chamber preference test	1	60 min	lever presses	Otobe and Makino 2004
examples for odor preference tests						
odor	stressed vs. nonstressed adult conspecifics	odor preference test	3?	10 min	no	Carr et al. 1980
	female- vs. male-soiled bedding (with or without the neurotransmitter 5-hydroxytryptamine)		2	5 min		Liu et al. 2011
	female- vs. male-soiled bedding (with or without serotonergic neurons)		2			Zhang et al. 2013
odor, genetics	male and female urine of mice with same or different genetic background		1			Angoa-Pérez et al. 2015
examples for novelty preference						
social contact	novel object (with or without Müllerian inhibiting substance)	novel object recognition test	1	5 min	no	Morgan et al. 2011

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category	comparison of	method	number of compartments	duration (test)	strength assessed	reference
pharmaceutics	novel object, novel environment (correlation with rewarding effect of cocaine)	novel object recognition test, novel environment test	1 or 2	10 min or 20 min	no	Vidal-Infer et al. 2012
genetics	novel environment (by mice with different genetic backgrounds)	novel environment	2	20 min	no	Kliethermes and Crabbe 2006
examples for social approach behavior tests (preference tests between familiar and unfamiliar companion)						
social contact	familiar vs. unfamiliar companion	T-maze	2 + center	5 min habituation + 10 min testing	no	Moy et al. 2004
	familiar vs. unfamiliar companion (under different lighting schedules)			10 min		Yang et al. 2007
	familiar vs. unfamiliar companion (autism model)			10 min		Chadman et al. 2008
	familiar vs. unfamiliar companion			10 min habituation + 10 min testing		Pearson et al. 2010
	validation of a social appraoch/recognition test (familiar vs. unfamiliar companion)			5 min		Macbeth et al. 2009
	validation of a social appraoch/recognition test (familiar vs. unfamiliar companion)			10 min		Kaidanovich-Beilin et al. 2011
	familiar vs. unfamiliar companion (autism model)			10 min		Carter et al. 2011
	familiar vs. unfamiliar companion (autism model)			?		Roullet and Crawley 2011
	typical' vs. 'atypical' companion (autism model)			30 min		Shah et al. 2013

time where the animal is most motivated. Automated T-maze apparatuses could reduce these issues and there are promising developments in this direction for alternation tasks (Choi 2018).

Home cage based preference test

Home cage based preference tests are often used to compare different cage conditions (Figure 2). Usually two or more cages are connected by alleys or tubes. In some studies there is a center cage from which the animal can explore other compartments and thereby choose where it spends most of the time. To keep track of the position of the animal, its movements are monitored either via infrared (IR) light barriers (Blom et al. 1992), video recording of the cages (Godbey et al. 2011), telemetry (Kawakami et al. 2012) or radio-frequency identification in the tunnels leading from one cage to the next (Kirchner et al. 2012). Here, preference is measured as time spent in the different cages. In some studies, it is also divided into active (during dark phase) and passive (during light phase) behavior (Lewejohann and Sachser 2000).

In comparison to the T-maze or the conditioned place preference, home cage based preference tests have the possibility to test socially living animals as a group (Gaskill et al. 2009). However, whether or not to test the animals together in a group should be weighed carefully. For example, one disadvantage of testing the animals in groups is that individuals might influence each other. Animals might change location to follow or avoid another group member. Thus, only dominant animals might be able to choose freely between options (as suggested by Blom et al. 1992, Manser et al. 1996). On the other hand, testing a socially living animal apart from the group might cause stress and affect the behavior. The resulting preferences then may not be transferable to the normal, group-housed husbandry situations (as suggested by Blom et al. 1992). A feasible approach might be to test the respective resources with single as well as with group housed animals and subsequently evaluate whether or not the preference changes in relation to the social condition (Lewejohann and Sachser 2000).

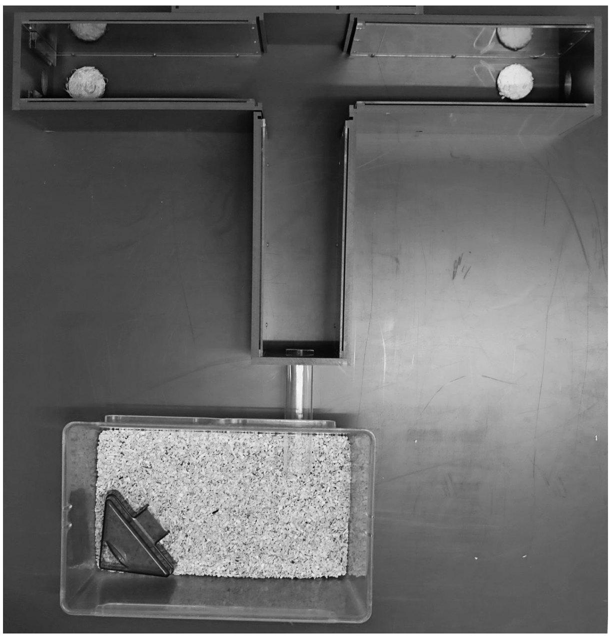

FIGURE 1: *T-Maze connected to a home cage. Mice can enter the maze through the tube and choose between resources provided in both upper arms of the T-maze.*

FIGURE 2: *Home cage based preference test. Mice can freely move between both cages through the connecting tube. Cage lids providing food and water ad libitum were removed for illustrating purpose.*

Another advantage of home cage based preference tests is the measuring of preference over a longer time period instead of a few minutes. Nevertheless, unlimited continuous access to all options has some limitations of which the experimenter should be aware. In preference tests, the animal is usually required to choose between two options. In this case, there is already a cost included, namely that one option is "sacrificed" in order to get the other, preferred option (Kirkden and Pajor 2006). However, if two options are presented simultaneously and with continuous access for the animal, this cost has now not to be procured: When getting deprived the animal can easily turn to the other option and the test apparatus might be perceived as one home with different compartments. To carry this consideration to extremes, preference for one option might not only influence the other but animals might not even perceive the options as separate (similar considerations in Patterson-Kane et al. 2001, Kirkden and Pajor 2006). Reinstating these costs would be possible, for instance, by introducing obstacles (see also section "Measuring strength of preference") or limited time windows in which the animals are allowed to make a new choice.

Conditioned place preference

If potentially aversive stimuli are to be tested, conditioned place preference (CPP) or conditioned place aversion (CPA) (Prus et al. 2009) might present a more suitable test design than T-maze preference tests or home cage based preference tests (Cunningham et al. 2006a): In the T-maze the animal may sit between both arms without choosing any of the unfavored options, while in the home cage based preference test the animal would be exposed to the aversive stimuli longer than probably necessary.

In general, for conditioned place preference the animal receives two alternating treatments followed each by spending time in one of two specific chambers. This procedure is repeated usually over several trials and days. By Pavlovian conditioning, the animal learns to associate environmental stimuli of one chamber with one treatment and the stimuli presented in the other chamber is associated with the other treatment. A variety of stimuli such as different bedding materials, lighting conditions, visual patterns or olfactory cues can be used as the conditioned stimulus. It has been shown that after successful conditioning the stimuli themselves (former neutral now conditioned stimuli) can indeed elicit rewarding effects without the unconditioned stimuli being presented as measured by dopaminergic efflux (Lin et al. 2007). In the final preference test, the animal gets access to both chambers and dwelling time in each chamber is used to assess preference (or lesser avoidance). Given the animal had no initial preference for one of the two chambers, a significant longer dwelling time in one chamber compared to the other is assumed to reflect a preference. However, it does not allow an inference on the actual strength of this preference.

There are several designs for test apparatuses for testing CPP. A simple form would be to use the same apparatus as for home cage based preference tests and present each of the respective stimuli in one of the two compartments. It has to be assured that the stimuli are indeed neutral (no preference for the one or the other) before conditioning (see also below, "Influencing factors"). If there is, however, a baseline preference for the one or the other compartment this can be used to design a biased CPP in which the prospectively less preferred resource or drug is paired with the formerly preferred stimulus in order to demonstrate that the CPP is stronger than the initial bias. Alternatively, tested resource-stimuli combinations can be randomized in order to dilute prior biases statistically (Prus et al. 2009).

CPP is often used to test for the effects of aversive or attractive drugs (Wang et al. 2014). However, in principle it is conceivable to modify the CPP paradigm for severity assessment by preference comparisons between behavioral measures, e.g., commonly used tests like the open field test, the elevated plus maze or the water maze.

Ranking of preference

In the test designs outlined above, preference can be tested by giving a binary choice between two resources. In principle more than two goods can be rated against each other by increasing the number of arms in the T-Maze (e.g., 8-arm maze) or by building home cage based preference tests with more than two cages being connected (Ago et al. 2002). Still, such measures would limit the number of goods that can be reasonably rated against each other.

To overcome such limitations in the determination of an animal's individual ranking, we propose a combination of multiple two-alternative pairings of various choices. For example, if given the choice, mice usually prefer almond flakes over oat flakes (Novak et al. 2016) or sugared milk over standard pellet food. In both choices one item is preferred over another but it is unclear how strong this preference is. However, by testing a number of different commodities in a row with systematic overlap of given choices one can derive a gradual scale (e.g., sugared milk > almond flake > oat flake > standard pellet food). However, some goods might not be compatible in a binary choice test especially if different motivational systems are involved. E.g., results from tests where mice would have to choose between nesting material and oat flakes will depend on saturation as well as on nest building motivation. As a consequence results would be misleading and thus such goods would not be feasible to be tested against each other. To ascertain the strength of preference between goods from different motivational systems a different form of ranking would be required.

Measuring strength of preference

A compelling approach to estimate the value of the choices made is to raise costs and compare the prices the animals are willing to pay. As stated above, if one option is preferred over another, the animal "pays" for this preferred option with the loss of the other option (Kirkden and Pajor 2006). However, for further comparison and scaling of preferences, the choices can be made more difficult by introducing obstacles (Sherwin and Nicol 1995). Thus, the costs can be increased and in testing if the animal is still willing to pay it, the strength of preference can be assessed more precisely. Typically used obstacles are, for example, physical obstacles or operant tasks.

Physical tasks can be, for instance, a grid floor in the cage where the preferred nesting material lies (Van de Weerd et al. 1998), an airstream, a gap, or a water tank placed in the way towards the option (Sherwin and Nicol 1995). Such obstacles can also be imposed in order to make it more costly to escape from a certain stimulus: In a test on social dominance the subordinate mice swam through a cage filled with water in order to escape attacks from the dominant individual (Lewejohann et al. 2010). Thus, this is not a simple preference for rather not being close to the rival, but the emigration is coming at the cost of swimming. Such choices can be made even more costly by increasing the distance to be swum or by introducing more obstacles.

Operant tasks are another, elegant way of introducing obstacles. With the help of operant conditioning techniques, mice can be trained to obtain goods only after performing a specific task, for example, making a nose poke (Atalayer and Rowland 2011, Atalayer and Rowland 2009), running in a wheel (e.g., Atalayer and Rowland 2011), pressing a lever (e.g., Atalayer and Rowland 2009) for a given number of times (fixed ratio, FR) or lifting a weight (Manser et al. 1998, Manser et al. 1996). The number of rewards obtained at increasing FR can be used to calculate consumer demand functions (Dawkins 1977). In brief, options for which an animal is willing to pay (e.g., press a lever) despite increasing price (increasing FR) are considered important necessities while goods for which an animal refuses to work the lever at increasing FR are considered luxury items. On the other hand, if aversive stimuli are compared, the price an animal is willing to pay to escape the treatment gives an insight into the strength of aversion. Also, the curve of demand can be used to compare the preference of different goods: In a home cage based test design, mice were trained to work a lever in order to get access to enriched housing conditions (Lewejohann and Sachser 2000). The system consisted of two cages that were connected by a tunnel. Mice pressed the lever up to 16 times for a single entry to an enriched cage. The number of accesses per day decreased as the fixed ratio was increased. However, comparing the demand for enrichment to the demand for getting access to a second empty standard cage revealed a significant difference with the curve for enrichment being less steep, thus indicating a higher demand for enrichment than for mere additional space.

Working for being exempt from measures such as handling, restraint, or swimming in a water maze, can be approached by first associating a compartment of a choice apparatus with these measures and subsequently measuring the price the mice are willing to pay for accessing or leaving the compartment. Using such approaches of combining CPP/CPA with consumer demand theory, mice could also be "asked" to rate the severity of experimental procedures themselves. However, while consumer demand theory has been used to rate a number of different commodities for mice such as additional space (Sherwin 2007) or access to conspecifics (Sherwin 2003), there is up to now no systematic approach using consumer demand to assess severity for experimental procedures.

Apart from obstacles, it would be possible to offer rewards to measure the strength of preference. Using classical conditioning, animals can be trained to associate a specific stimulus with a reward. For example using Pavlovian conditioning a formerly neutral odor (clove oil) can be presented along with a preferred food (cereals) and become a conditioned stimulus associated with the reward (Johnson and Wilbrecht 2011). Using these conditioned animals in preference tests would allow combining less preferred options with stimuli predicting a food reward. If the addition of a positively associated odor is sufficient to shift the preference, the difference between the tested goods is consequently less than the added value introduced by the odor. Thus, if the preferences for different kinds of food are known, strength of preference could be assessed by testing which food would be necessary to "bribe" the animal into choosing the formerly less preferred option.

Finally the number of trials needed for successful conditioning in CPP/CPA might also indicate the strength of the rewarding or punishing properties of the tested resources (Prus et al. 2009). This also has to be evaluated with regard to its feasibility for severity assessment. Overall, it is thus a timely and congenial approach to transfer these techniques for an in depth analysis of severity assessment from an animal's point of view.

Influencing factors

When designing a preference test, there are a few factors the experimenter should keep in mind. A number of these are discussed in more detail in the following.

- Preferences can be affected by prior experience the animal has gained with the respective goods to choose from (Arnold and Estep 1994). Especially when only one good is previously known further experience of both options can change preference based on novelty seeking or risk aversion (Dawkins 1977). For this reason, when performing preference tests it is important that the animal has already experienced both choices equally. In the case of both options being unknown to the animal at first, this can be achieved through a sampling phase prior to the preference test (for examples in T-maze tests see Deacon and Rawlins 2006, Pioli et al. 2014).
- The habituation to the apparatus plays an important role, especially when working with mazes unknown to the animal. An animal that is not habituated long enough to the apparatus will probably show a slower performance (Deacon and Rawlins 2006) and thus will not perform reliably. Moreover, insufficient habituation can result in elevated stress symptoms which in turn may lead to impaired memory performance (Okuda et al. 2004) and affect the results. Therefore, time and care should be invested in habituating the animal to the apparatus.
- The spatial location of the options might influence the preference. For example, an animal might have a side bias (e.g., always choosing left in a T-maze)

or a preferred position in the room (e.g., noise, light, air flow, facing more to the wall or the open). To rule these factors out, it is suggested to change the position of the apparatus during experimentation (Blom et al. 1992, Godbey et al. 2011). If performing CPP, however, change of location is not always advisable. Here, the spatial information could work as an additional stimulus (Cunningham et al. 2006b, Cunningham and Zerizef 2014). If such preferences for unknown features of the testing facilities cannot be ruled out, it should be tested for spatial bias beforehand and/or randomized between individuals.

- Odors can have an impact on the preference. It has already been shown that the sex of the experimenter has an influence on behavioral tests, with male experimenters alone probably inducing more stress in the animals (Sorge et al. 2014). In addition, especially regarding the T-maze the olfactory cues of preceding animals might have an influence on the path the subsequent animal chooses: Rats, for example, are able to track the odors of themselves and other rats (Wallace et al. 2002) and although odor cues did not seem to influence their performance in an elevated plus maze (Olton and Collison 1979), it was observed that rats use intraspecific odor cues on the barrier for orientation in a water-escape T-maze task (Means et al. 1992).
- It is important whether the option itself or a conditioned stimulus representing the option is provided during the test. Especially if the animal could be easily saturated by access to the actual option it would be wise to use a conditioned stimulus instead. Also, if the animal is required to choose between treatments (as for instance in CPP), a conditioned stimulus is more advisable. Yet, the kind of stimulus best to use is also an important decision. Olfactory cues are probably the most effective, working even for rat pubs (Cutuli et al. 2015) and fruit flies (Fujita and Tanimura 2011). Apart from that, for mice tactile cues (e.g., structure on the floor) tend to be more effective than spatial cues (e.g., left or right) and these again more effective than visual cues (e.g., stripes on the floor) (Cunningham et al. 2006b).
- If a conditioned stimulus is used, the chosen stimulus has to be within the sensory capabilities of the tested species. What is more, the association between stimulus and the respective option must be biologically meaningful to some extent or, in the words of Seligman (Seligman 1971), there has to be a minimum "preparedness" for the association. This phenomenon is best illustrated by the classical experiments of Garcia and Koelling: It could be shown that rats can associate nausea (induced by x-rays) with flavoured water but not with an auditory or visual cue. Vice versa, auditory or visual cues could be easily conditioned to avoiding electric shocks but flavoured fluid could not (Garcia and Koelling 1966). In addition, not only species but also strains may differ with regard to sensory capabilities and behavior. For example, DBA/2J mice show a deficit in trace fear conditioning in comparison to C57BL/6J and 129S6 mice (Holmes et al. 2002).
- Moreover, learning and memory functions are crucial for the detection of a specific preference. In a test based on recently learned information (which is the case for T-maze and conditioned place preference tests but not necessarily for home-cage based preference tests), animals with learning or memory deficits may not show a distinct preference, although they might have one (Galea et al. 2001). Also, it was found that enhancing memory by providing a sucrose solution affected conditioned place preference (White and Carr 1985).

Tests on emotional valence

Preference tests are a valuable method to investigate what goods mice choose or what actions they prefer to take. However, in animal experimentation subjects usually cannot choose between taking part in an experiment or avoiding experimental procedures at all. Moreover, procedures in animal experimentation which are known to be rated severe (e.g., neuropathic pain, inescapable electric footshocks) certainly do not call for preference tests as the outcome would be overly predictable. Discomfort due to involuntary participation in experiments might, however, leave traces in internal affective states. Apart from being picked up and put into a test apparatus, the severity of the specific experiment is expected to be reflected by changes of the affective state. Such emotion-like states are, however, usually not obvious to others. Especially in species which evolved under significant predatory pressure like mice, it is likely that selection pressure has worked against revealing signs of vulnerability in order to be less conspicuous to predators. Nevertheless, it has been shown in mice that cage mates can interpret and share the affective states of others, showing a form of empathy (Gonzalez-Liencres et al. 2014). Overall, there is no serious doubt that animals have affective lives (Panksepp 2011) and it has been shown that affective states are indeed measurable. In animal experiments, a vast number of experimental paradigms designed for revealing the emotional states of laboratory mice is focusing on anxiety-like behavior (Belzung and Griebel 2001). An often used test to measure anxiety-like behavior is the elevated plus maze (Lister 1987). Rodents have a natural aversion for open spaces, which is used in this test. The plus maze has two closed and two opened arms. To measure the anxiety-like behavior the number of entries into the closed arms compared to the entries into the opened arms and the time spent on the arms are measured. The more entries or time spent on the open arms, the less anxiety-like the animal is considered to be. Housing conditions, social experience as well as the experimental treatments shape the behavioral profile of mice used as animal model for human disease over a lifetime (Brust et al. 2015). While some treatments have very obvious effects on the affective state of the animals, other conditions might have only subtle effects. Especially for more subtle effects a drawback of experimental procedures like the elevated plus maze is that subjecting a mouse to the test apparatus in itself is also aversive and would interfere with the desired measurements. In addition to measuring anxiety-like behavior in mice, affective states were traditionally inferred from stress physiology such as blood pressure, heart rate, and glucocorticoid stress hormones measured in blood or feces samples (Bodden et al. 2015, Koolhaas et al. 1999).

Measuring the valence of the goods tested in preference tests is less well established. Stress physiological reactions after being exposed to a test situation might

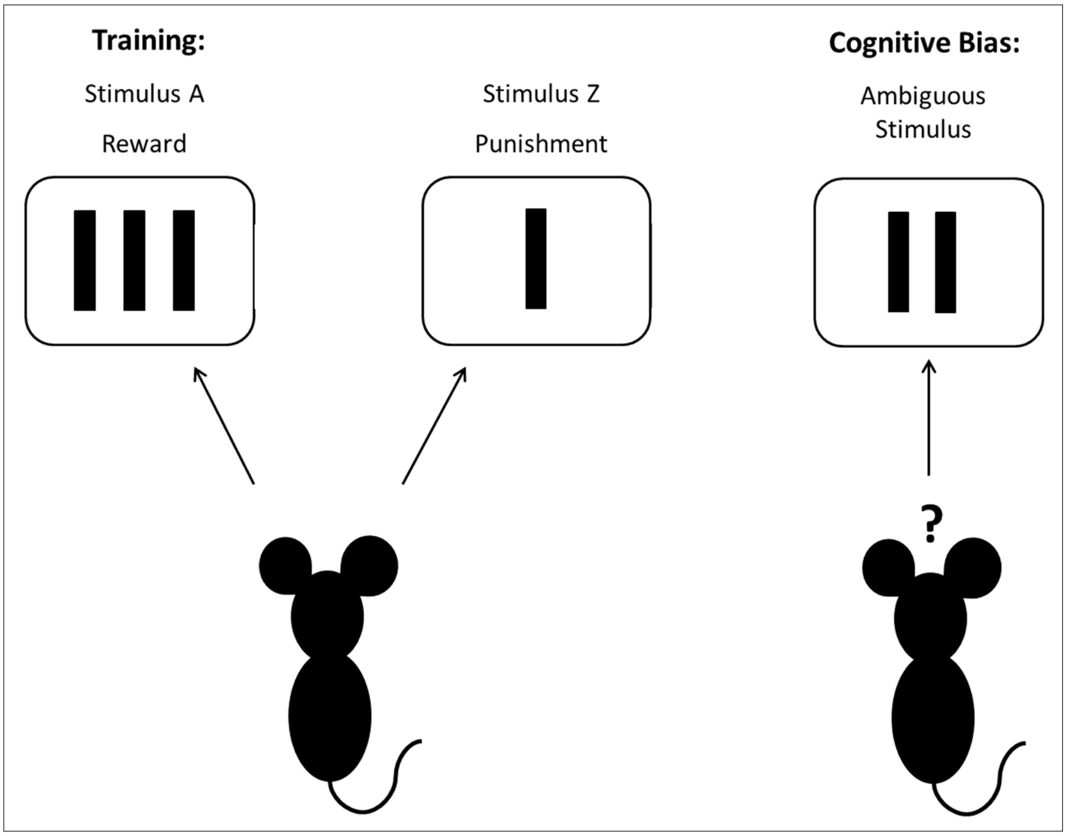

FIGURE 3: *Cognitive Bias Test. Training: During the training phase the animals have to learn which stimulus is associated with a reward and which stimulus is associated with a punishment. In this example stimulus A indicating a reward while stimulus Z is followed by a punishment. Cognitive Bias: After successfully conditioning the subject, an ambiguous stimulus is presented. This ambiguous stimulus is calibrated between stimulus A and Z. The reaction towards this ambiguous stimulus is measured with regard to approach or avoidance as well as the respective latencies.*

give a hint on how exciting or fear inducing such an exposure is being perceived. However, increased stress hormones alone do not provide any information on whether or not the situation is perceived as positive or negative. For example many social interactions trigger elevated stress hormone titers (Harding 1981) and it is known that also positively valenced events such as prospective matings induce stress (Tamanini et al. 1983). Thus, a more comprehensive consideration on how certain conditions and test procedures influence the affective state of an animal would be highly valuable. In 2004, cognitive bias, the altered information processing resulting from an individual's background emotional state, has been suggested as a promising new indicator of animal emotion (Harding et al. 2004). Noteworthy, the cognitive component of emotion has remained vastly unexplored in animals for a long time. Cognition allows animals to gather, process and store information from the environment and refers to learning, memory, as well as decision making (Herrmann and Call 2012). Cognitive Bias tests investigate how decisions depend on the expectation of future events. Experimental paradigms are based on the idea that individuals in a putatively negative emotional state are more likely to judge an ambiguous stimulus as if it predicts a negative event. Vice versa, individuals in positive emotional states are more likely to be optimistic (Mendl et al. 2009).

Cognitive Bias Test

The basic principle of the cognition bias test is to condition the animals to scalable stimuli like auditory, visual or spatial stimuli (Figure 3). These stimuli are connected to a reward or to a punishment. A reward could be for example food, water or access to the home cage, whereas white noise, an air-puff or an electric food shock could serve as a punishment. After conditioning, an ambiguous stimulus is presented, which is calibrated between the positively and negatively associated ends of the scalable stimuli. The animal's reaction towards this ambiguous stimulus is measured with regard to approach or avoidance as well as the respective latencies. If the animal is in a positive emotional state, the reaction towards this ambiguous stimulus will be fast and if the animal is in a negative emotional state, the reaction will be hesitant. Overviews and critical methodological aspects of cognitive bias tests can be found in (Bethell 2015, Gygax 2014).

Harding and colleagues (2004) created the cognitive bias test for rats first. The rats were trained to press a lever when one tone was presented to get a reward (food) and to refrain from pressing a lever when another tone was presented to avoid a punishment (white noise). After this operant discrimination task the rats were housed in unpredictable housing conditions (including reversing dark/light cycle, dampening bedding, and odors of unfamiliar conspecific) to measure the effect of prospectively unfavorable housing conditions on the emotional state. Following the housing manipulations the cognitive bias test was conducted with the presentation of an ambiguous tone. This tone was calibrated between the trained tones for reward and punishment. Indeed, rats which were housed under unpredictable conditions pressed the lever delayed and fewer times than the control group. This indicates that unpredictable conditions influence the emotional state of rats and render them to be more "pessimistic".

Further cognitive bias tasks were created for different animal species. A visual discrimination task was created by Bateson and Matheson (2007) for European starlings (*Sturnus vulgaris*). The birds were trained to discriminate between a white and dark grey lid of a dish. Under a white lid a palatable mealworm was hidden, under the dark grey lid an unpalatable one. After training the birds were offered different lids of different shades of gray. Birds which were first housed in enriched cages and then transferred to standard cages showed more pessimistic behavior than birds which were first housed in standard cages and then transferred to enriched cages. These results correspond with the results from Harding and colleagues. They assume that in an unpredictable and potentially dangerous environment it could be better for the animals to react more conservative to unknown situations to ensure survival (Bates and Matheson 2007).

Although mice are the premier mammalian model system in biomedical research it took quite some time until the first cognitive bias tests for mice were presented. In 2012, an olfactory based test was presented in which pieces of palatable and non-palatable almond were associated with certain smells (Boleij et al. 2012). Mixtures of both odor cues were explored more cautiously by one strain of mice while a different strain showed no such discrimination. Kloke and colleagues established a spatial cognitive bias test for mice (Kloke et al. 2014). In their protocol mice were trained to associate different arms of a labyrinth with either a reward (access to home cage) or a mild punishment (air-puff). In the final cognitive bias trial the mice could choose ambiguous arms located between the previously rewarded or punished arms. Optimistic mice approached ambiguous arms quickly while pessimistic mice hesitated to approach unknown arms. Another spatial cognitive bias test for mice was created by Novak and colleagues. They used an eight arm maze for an exploration based test. Two adjacent arms were associated with a reward (darkness and food) and the two arms on the opposite were associated with a punishment (light and white noise). After training the mice were handled either by tail handling or by cupped handling. During the cognitive bias test all eight arms of the maze were available to explore and both groups showed a similar pattern of exploration behavior (Novak et al. 2015). The same paradigm was used to examine the influence of different stereotypic patterns on animal welfare in mice. The results indicate that the effects of stereotypies on animal welfare are dependent on both, the type of stereotype and the strain of mice (Novak et al. 2016).

Go/no-go versus go/go task

An often discussed problem of the classical go for reward and no-go to avoid a punishment approach is that the no-go behavior could also be caused by a reduced motivation and activity and not by a pessimistic emotional state (Enkel et al. 2010, Matheson et al. 2008). Consequently, some cognitive bias tests were created in which the animals always have to be active to get a reward or to avoid a punishment. For example, rats had to press a lever for one tone to get a food reward and had to press another lever upon another tone to avoid an electric food shock (Enkel et al. 2010). In another active choice test mice were trained to discriminate between different grades of sandpaper. The test apparatus contained a start box and two separated compartments connected to the start box. Within these compartments food of different quality (as assessed by choice tests) was presented. The mice had to go actively to these compartments to get the reward (Novak et al. 2016). Noteworthy, here and in comparable studies a punishment was waived as the animals could choose between two rewards differing with regard to their rewarding strength (Novak et al. 2016). Such a design avoids repeated punishment during the training phase which could have a negative effect on the emotional state (Brydges et al. 2011). In addition, not including punishment has been shown to lead to a faster training success (Parker et al. 2014) and a cognitive bias test without punishment should be better suited to determine the positive emotional state (Mendl et al. 2009). However, omitting punishment comes at the price that making a wrong decision might not be costly enough and thus results could be interpreted as overly optimistic.

Cognitive bias tests have been used to examine the affective state of animals following influence of environmental factors such as enriched vs. not-enriched or unpredictable housing conditions. Indeed such housing conditions have an influence on the emotional state of animals. Moreover, cognitive bias tests have been used for the better understanding of the impact of juvenile and chronic stress (Brydges et al. 2012, Chaby et al. 2013). Based on this evidence we propose a cognitive bias test as a valuable method for animal welfare research and for severity assessment of testing conditions.

Home cage based operant tests

Unfortunately, most published protocols for testing affective biases in mice (Graulich et al. 2016, Boleij et al. 2012, Novak et al. 2016) are labor intensive and face considerable drop-out rates. Furthermore, none of these are feasible for repeatedly testing the same individuals without an enormous expenditure of training time. In addition, the animals are usually removed from their home cage and have to be manually transferred into the test apparatus. During this time the animals are separated from their social group and they are in a new unknown situation. All of this could have an impact on the emotional state whereby the results could be influenced by procedural features of the testing itself. A new method to circumvent these influences could be an automated, home cage based operant test.

One automated operant conditioning test was created by de Hoz and Nelken in 2014. They used an Audiobox to measure discrimination and generalization for tone frequencies in mice (de Hoz and Nelken 2014). The test chamber where tones were presented was connected through a corridor to the home cage. Water was present only in the chamber upon performing a task while food was present ad libitum in the home cage. Each mouse could choose freely when to go to the Audiobox for the task and to get access to water, thus there was no influence of the experimenter. Another automated operant conditioning system is the Psibox (Francis and Kanold 2017). This box allows training mice within two weeks independently and simultaneously in their home cage to receive water contingent upon an auditory detection task. It has been shown that Pavlovian conditioning to an auditory stimulus associated to a food reward in a home cage based design can be obtained even within 24 h (Wistuba et al. 2017).

Similar to home cage based operant conditioning systems, home cage based cognitive bias tests are needed to overcome many of the disadvantages of the test paradigms currently used. In contrast to traditional cognitive bias tests in which the animal has to be placed in a separate apparatus for a specific period of time, in an automated test this is not necessary. The animals can be trained in their home environment without being separated from their social group. In addition, the animals can more or less freely schedule when to conduct the test if the test system is connected with the home cage for the whole time of the experiment. This would allow the animals to be tested in their natural active phases according to their circadian rhythm. This in turn is likely to have a positive impact on the success of conditioning and shorten the training period. Additionally, an automated home cage "based" cognitive bias test system would reduce interference of the experimenter and the same animals could be tested multiple times with less expenditure of time, because the re-training can be carried out in the automated test system.

Conclusion

The review discusses two main approaches to assess severity from an animal's point of view: Preference tests, which investigate the preference of the animals by asking them to choose one out of two or more options, and tests on emotional valence, which can monitor changes in the emotional state of the animal. Both approaches were already used in animal welfare related studies, for example, in the assessment of housing conditions. However, the full potential of these methods for severity assessment from an animal's point of view is still to be explored. Moreover, most cognitive bias tests focus on a shift to a more pessimistic like state following worsening the conditions an animal is living in. One intriguing approach would be to find out what changes can be made in order to shift cognitive bias towards a more optimistic future expectation in order to significantly improve animal welfare.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

Not applicable (no original data derived from previously unpublished animal experimentation was included in this review).

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Authors contribution

AH, PK, KD, and LL contributed to the design and implementation of the review, to the literature research, and to the writing of the manuscript.

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