Research report

Evidence for a relationship between cage stereotypes and behavioural disinhibition in laboratory rodents

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Abstract

Cage stereotypes—abnormal, repetitive, unvarying and apparently functionless behaviours—are common in many captive animals, sometimes resulting in self-injury or decreased reproductive success. However, a general mechanistic or neurophysiological understanding of cage stereotypes has proved elusive. In contrast, stereotypes in human mental disorder, or those induced by drugs or brain lesions, are well understood, and are thought to result from the disinhibition of behavioural selection by the basal ganglia. In this study, we found that the cage stereotypes of captive bank voles also correlate with signs of altered response selection by the basal ganglia. Stereotypic bar-mouthing in the caged voles correlated with inappropriate responding in extinction learning, impairments of response timing, evidence of a knowledge-action dissociation, increased rates of behavioural activation, and hyperactivity. Furthermore, all these signs intercorrelated, implicating a single underlying deficit consistent with striatal disinhibition of response selection. Bar-mouthing thus appears fundamentally similar to the stereotypes of autists, schizophrenics, and subjects treated with amphetamine or basal ganglial lesions. These results represent the first evidence for a neural substrate of cage stereotype. They also suggest that stereotypic animals may experience novel forms of psychological distress, and that stereotype might well represent a potential confound in many behavioural experiments. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Stereotypes are repetitive sequences of motor behaviour that are topographically and morphologically invariant, often rhythmical, and apparently purposeless (e.g. [8,18,45,58]). They are commonly displayed by zoo, farm and laboratory animals. For example, stereotypes like bar-mouthing are widespread in rodents caged as research models, including laboratory mice [50,77], chinchillas [34], black rats [11], deer mice [58], field voles [21], and bank voles [12,14,21]. They are also sometimes extremely prevalent (present in ca. 98% of male ICR mice: [77]). Such ‘cage stereotypes’ are typically elicited by the frustration of specific motivated behaviours (e.g. [49,62,70]), in combination with stress

(e.g. [9,75]) and a reduction in behavioural competition caused by low environmental complexity (e.g. [29,66]). However, although the causation of particular cage stereotypes is fairly well understood at the motivational level (e.g. [70,77]), a more general neurophysiological understanding of these behaviours is lacking. Thus while dopaminergic and opiate receptor antagonists (e.g. [33]), and a variety of serotonergic agents [35,57], are all known to suppress cage stereotypy, evidence for baseline alterations in neurotransmitter function is inconsistent (e.g. [54,58]). This may indicate that multiple neurotransmitter systems are involved, just as they are in drug-induced stereotypy (for review see: [9,25,28,65]), or that, rather than the transmitter levels and receptor densities most commonly measured (e.g. [54,58]), subtle aspects of the systems are implicated such as receptor sensitivity (e.g. [6,58]).

This lack of a consistent neurophysiological understanding of cage stereotypes is in marked contrast with

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other forms of stereotypy (for review see [25]). All clinical, drug- and lesion-induced stereotypies for which a neural substrate is known, involve altered function in the dorsal striatum that causes reduced behavioural inhibition. For instance, dopamine D₂ receptor agonists such as amphetamine induce a general disinhibition of behaviour that culminates in stereotypy [9,40,68]. Stereotypies induced by amphetamine are mediated by their action in the dorsal basal ganglia (e.g. [32]). Similarly, isolation-rearing induces both stereotypy and changes in basal ganglia dopaminergic tone [36,37,42], as does premature weaning [24,63]. Basal ganglia lesions in humans are similarly associated with stereotypy-like behaviour [1,39]. Stereotypy is also a common sign in disorders such as autism and schizophrenia [23,56,67]. In autism [67] and schizophrenia [23], the severity of stereotypy correlates with impairments on tasks designed to detect the unique signs of dorsal basal ganglia dysfunction. Stereotypies also correlate with the inappropriate repetition of words in schizophrenic speech [41]; and in schizophrenia other ‘disorganised symptoms’ (e.g. unpredictable agitation, ‘derailment’, ‘tangentiality’ in thought and speech, and disinhibited or fragmented behaviour: [4]) may be related to the disinhibition of responses characteristic of dorsal basal ganglia dysfunction [17]. In all of these examples, the precise cellular mechanisms vary, but the systems-level dysfunction causing stereotypy is essentially the same [1,25,28,65,67,69].

The ubiquitous association of stereotypy with dorsal basal ganglia dysfunction is consistent with the essential role this structure plays in the motor system (c.f. [1,52,66]). Thus the selection and sequencing of normal behaviour and movement is regulated by the interaction of two agonistic cortico-striatal circuit loops, running through the dorsal basal ganglia [1,3,60]. The first, ‘direct’, pathway activates motor programs, whilst the second, ‘indirect’, pathway is inhibitory, acting to allow the proper transition between competing programs. Each pathway is regulated by different neurotransmitters or receptor subtypes. Thus dopamine D₁ receptors are concentrated in the direct pathway, whilst dopamine D₂ receptors are concentrated in the indirect pathway; and within-circuit negative feedback is provided by dynorphin releasing neurones in the direct pathway, and enkephalin releasing neurones in the indirect pathway (for review see: [2,25,28,65]). Thus lesions or drugs affecting the direct pathway (e.g. agents acting selectively at the dopamine D₁ receptor) lead to a general activation or suppression of all behaviour [1,68], while lesions or drugs affecting the indirect pathway (e.g. agents acting selectively at the dopamine D₂ receptor, or opiate agonists acting on receptors sensitive to enkephalin) selectively induce or suppress stereotypy [1,38,68]. Overall, the vast variety of drugs that can induce stereotypy, therefore, do so via suppressing

indirect pathway activity, often (though not always: see [19]) by influencing its dopaminergic regulation.

If drug- and lesion-induced stereotypies seem to involve a systems-level disinhibition of behaviour, via the suppression of the inhibitory influence of the indirect pathway, could this also account for cage stereotypies? A similar dysfunction in cage stereotypy would have important ethical and animal welfare implications (e.g. [5]), as well as implications for the use of laboratory rodents as valid research models (e.g. [72,73]). Furthermore, four features of cage stereotypy do suggest that the behaviour may reflect impaired function. First, the long-term effects of abnormal rearing conditions on cage stereotypy suggest that the behaviour may reflect altered CNS development. For example, in bank voles and black rats, stereotypies do not appear in caged animals wild-caught as adults, only in laboratory-reared subjects [11,12]; and in mice and mink, they are most prevalent in early-weaned animals [43,76]. Second, several observations suggest an underlying change in behavioural organisation: as stereotypies develop, they become increasingly hard to abolish with opioid antagonists [33] and environmental enrichment [14,47]; and stereotypic animals also sometimes show reduced behavioural responsiveness to external stimuli (e.g. [13,71]). Third, stereotypies can cause reduced physical health to the performer or its offspring. For example, cage stereotypies may result in self-injury in many species (e.g. [53]), or deficits in maternal behaviour that impair the growth (e.g. [46]) or increase the mortality (e.g. [64]) of offspring. Fourth, treatments which enhance the development of cage stereotypies [45] also induce widespread changes in the brain, and a general disinhibition of behavioural responses in rodents [48,61]. Taken together, these studies argue for a role of dysfunctional behavioural organisation in cage stereotypy. However, to date, quantitative investigation of this possibility has been lacking.

We therefore investigated the role of basal ganglia dysfunction in rodent cage stereotypy, by measuring the behavioural correlates of bar-mouthing. Since they stem from decreased behavioural inhibition, stereotypies caused by clinical or experimentally-induced basal ganglia dysfunction form part of a suite of changes in behaviour. These include enhanced rates of behavioural initiation [20,40]; ‘impulsivity’ [59]; impaired performance in tasks where responses must be suppressed or slowed [20,40,59]; the inappropriate repetition, or ‘perseveration’ of previous actions [20,39], which impairs performance in tasks such as extinction learning [23,31,48,67]; and a concurrent knowledge-action dissociation in such tasks, whereby human subjects know (and report) the correct response to make but are unable to suppress automatic repetition of a previous, incorrect response [67]. Thus along with stereotypies, isolation-reared primates show poor abilities to suppress inap-

propriate behaviour in extinction [7,27], while the stereotypy frequencies of human subjects with autism and schizophrenia correlate with their inappropriate repetition of responses in gambling or sequence-generation tasks [23,67]. If rodent cage stereotypies are similarly indicative of altered central functioning, then they too should correlate with similar signs of impaired behavioural inhibition. We tested this hypothesis using bank voles, a convenient murid model of cage stereotypy [12,33].

2. Materials and methods

2.1. Subjects

Eight laboratory-bred bank voles (*Clethrionomys glareolus*) were singly housed from weaning at 21 days of age in opaque plastic mouse cages (32 × 20 × 19 cm) with sawdust bedding and ad libitum pellets and water, on a 14-h light:10-h dark cycle. Animal housing, care, and use was in accordance with UK Home Office, and institutional (Zoology Department, Oxford University, UK) guidelines.

2.2. Video observations

Bank voles are active throughout the 24-h day in a series of activity cycles lasting approximately 4 h [53]. This feature of their behaviour makes them particularly suitable subjects for behavioural work. Thus continuous video was recorded from 10:00 to 18:00 h (i.e. during lights-on), to ensure capturing at least one activity cycle. The first 4 h of activity (i.e. all non-sleep behaviour) on the tape were observed, and stereotypy recorded using a one-zero method with 30 s intervals, to find the proportion of total activity spent stereotyping. All animals performed a 'bar mouthing' stereotypy, where the animal held the cage bar in the diastema, and made a series of sham biting movements along the bar. These biting movements are idiosyncratic and conserved within individuals, both in their form, and in the cage location where they are performed [25,50,51,77].

2.3. General analytical methods

General Linear Models (GLM) were employed throughout. Suitable transformations were applied where necessary to meet the assumptions of parametric methods (normality of error, homogeneity of variance, and linearity). Further details are provided for each experiment below. All tests are one-tailed because in all cases the sign of the correlation was predicted, and the opposite sign would falsify our hypothesis.

2.4. Rate of behaviour initiation

In amphetamine-induced stereotypies, stereotypy is the endpoint of a process in which the inhibition of competing behavioural responses is reduced and lost, and the switching between behaviours becomes so rapid that only the most predominate behaviours can be initiated, until a single behavioural element is being continuously repeated. Thus as stereotypy emerges, the rate at which individuals switch between behaviours increases [40]. If cage stereotypy involves a similar mechanism, then the amount of stereotypy performed by an individual should correlate with the rate at which it switches between all behaviours.

The ethogram of behaviours in the bank vole is described in [25]. For each animal, four periods, each of 4 min continuous activity, were chosen at random from the 8 h of continuous video described previously. To ensure that the analysis compared like-with-like for low and high stereotypy animals, two 4-min periods when stereotypy was performed, and two when no stereotypy was performed were selected for each animal (using the one-zero data recorded previously). Thus independent of the overall stereotypy score of the animal, the videos selected for intensive observation were as similar as possible in terms of stereotypy. Stereotypy was included as a behaviour to switch between; this ensured a conservative test of the hypothesis because if stereotypy is a confound due to the 'blocking' of other activities, then it will reduce rather than inflate the magnitude of the relationship predicted.

The total 16 min for each animal were observed using continuous recording. Each time a bout of behaviour was initiated was counted as one initiation, regardless of the previous behaviour, for instance the sequence 'Feeding–Drinking–Drinking–Locomotion–Grooming–Nestbuilding' contains five initiations, as the vole paused between the two drinking bouts. However, in order to compare like with like, initiations of sub-elements within a behaviour chain were not counted (e.g. transitions between individual grooming movements were not counted). The mean number of behaviours initiated per minute was calculated, and correlated with stereotypy. The analysis was partialled for sex.

2.5. Maze tasks

Damage to the dorsal basal ganglia leads to a general tendency to inappropriately repeat previous responses, called recurrent perseveration [39,52,67]. Recurrent perseveration, as measured on a number of tasks, is also correlated with stereotypy in both schizophrenic [23] and autistic [67] patients. We therefore predicted that cage stereotypy would correlate with a general tendency to repeat previous responses. We measured

this tendency by examining the ability of each subject to suppress a previously learnt response in a spatial extinction task (c.f. [31]).

The maze was constructed from transparent plastic tubing, and was mounted on the home cage. The home-cage was moved to a separate room for testing. The tasks were run automatically by computer, which collected all data, and dispensed rewards as appropriate. The tasks were run over consecutive sessions, each lasting between 20 and 40 trials. Upon entering the maze from the home cage, subjects chose between one of two corridors. Each corridor contained a glass nozzle that could deliver 0.015 ml 10% w/v sucrose solution reward. One-way doors prevented the vole from back-tracking on itself. Each corridor exited via a one-way door back into the home cage. Infrared photobeams monitored the position of the animal in the maze (Fig. 1). Voles were food deprived for 6 h before testing. In the spatial discrimination task one corridor was rewarded (chosen at random for each animal at the start of the experiment, and balanced within sex). The criterion for completion of spatial discrimination was set at choosing 18/20 correct over three consecutive trials.

Once criterion was attained, extinction learning was assessed. In the extinction task, neither location provided reward. Criterion was now choosing at chance (13/20 or less for three consecutive trials). The number of trials to complete the extinction tasks was then correlated with stereotypy; this analysis was partialled for (i.e. statistically controlled for) sex and the number of trials taken to learn the spatial discrimination. Spatial discrimination and extinction learning involve a variety of common psychological processes. However, the key difference between these tasks is the inhibition of the response in extinction learning—a process known to involve the basal ganglia. Therefore, including spatial discrimination performance in the analysis allows each vole to act as its own control, explicitly removing the effect of common processes (e.g. motivational, perceptual, hedonic, or associative) and providing a pure measure of the unique feature of extinction—namely the inhibition of responses.

When rats learn a simple discrimination they make correct choices rapidly, but make incorrect choices after a longer latency [55]; amphetamine treated animals, however, fail to suppress rapid responding when it is made inappropriate [59]. We therefore used response latencies in extinction to see how readily our subjects suppressed rapid responding in the previously correct side of the maze. We predicted that stereotypy would be correlated with an impairment in the suppression of rapid responding. ‘Latency to choose’ equals the time between crossing the photobeam at the maze entrance, and the photobeam at the entrance of the chosen corridor. The mean latency to choose the incorrect

side of the maze over the previous 20 trials was divided by the mean latency to choose the correct side of the maze, (R). The criterion for divergence of choice latencies during learning was defined as $R > 2.0$ for three trials, and the criterion for convergence of latencies in extinction was defined as $R < 1.1$ for three trials. Stereotypy was correlated with the number of trials taken to show convergence of choice latencies in extinction. The analysis was partialled for sex and the number of trials taken to show a divergence of choice latencies during spatial discrimination (to control for motivational, perceptual and learning differences).

These data were then used to investigate evidence of a knowledge-action dissociation. Stereotypic human patients, and those with basal ganglia pathology, show a discrepancy between two behavioural signs of knowledge: verbal reports, and performance in knowledge-dependent tasks [39,67]. Our subjects similarly demonstrated two behavioural signs of knowledge: the nature and the latencies of their choices. In extinction, knowledge of the task is demonstrated both as choices return to chance, and as the latency to choose the previously correct side increases to match that of the previously incorrect side. The dissociation between these two behavioural signs of knowledge was therefore quantified by the magnitude of this latency increase at the point where the animal had successfully reverted to choosing at chance (see Fig. 2). We therefore predicted that the magnitude of the increase in the latency to choose the previously rewarded side of the maze would be negatively correlated with stereotypy. This analysis was partialled for sex, and the increase in the previously

Fig. 1. The maze apparatus (see text for a detailed description). The maze was mounted on top of the home cage. The apparatus was monitored and controlled by computer. Thus multiple trials could be run without the experimenter interacting with the vole.

Fig. 2. The theory behind demonstrating a knowledge-action dissociation in extinction. The solid line represents the latency to choose the previously unrewarded side of the maze, the dashed line the latency to choose the previously rewarded side, and the dot-dashed line the current score. In both figures the point where the animal reaches criterion on choices (i.e. is responding statistically at chance, and so must 'know' that it will not be rewarded) is indicated, and the increase in latency to choose the previously rewarded side of the maze is taken directly from the curve. (a) depicts an animal showing a large increase in latency at this point, thereby expressing knowledge of the absence of reward in latencies. (b) depicts an animal showing a small increase in latency to choose the previously rewarded side of the maze. Thus, despite showing that it understands that it will not be rewarded by its choices, the animal appears not to 'know' that it will not be rewarded when the latencies of these choices are examined. Thus the increase in this latency at the point where each animal is choosing the two sides of the maze at chance, directly measures the dissociation between the knowledge expressed in these two measures. Low stereotypy animals are predicted to show agreement (a), whilst high stereotypy animals are predicted to show dissociation (b).

incorrect choice latency. This latter covariate controls for individual differences (for instance in motivation), and the fact that latencies to choose tend to increase for both sides of the maze during extinction.

2.6. Home cage activity

Infrared beams were placed across the drinker and the cage lid, away from locations or routes associated with the stereotypies. The total number of beam breaks

between 17:00 and 10:00 h was recorded, and the mean number of beam breaks per minute calculated. Stereotypy was square-transformed to correct non-homogeneity of variance. The analysis was partialled by sex.

3. Results

3.1. Stereotypy

Individuals differed in the proportion of active behaviour spent in stereotypy, ranging from 3.5 to 28.1%. The most stereotypic animals also occasionally displayed a high-frequency tremor of the limbs when climbing the cage lid.

3.2. Rate of behaviour initiation

To test the prediction that stereotypy correlates with a generally increased rate of initiation of all behaviour, we analysed homecage behaviour. As predicted, the mean rate of behaviour initiation was positively correlated with stereotypy (GLM: $F_{1,5} = 19.38$; $P = 0.0035$) (Fig. 3).

3.3. Maze tasks

The number of trials to acquire the spatial discrimination (SD) was uncorrelated with stereotypy. However, as predicted, stereotypy was positively correlated with the number of trials taken to complete the extinction task (GLM, partialled for sex and SD: $F_{1,4} = 77.29$; $P = 0.0005$) (Fig. 4). Whilst the least stereotypic animal extinguished in 26 trials, the most stereotypic animal took 244.

Fig. 3. Stereotypy is positively correlated with the spontaneous rate of initiation of all behaviours in the homecage (GLM; $F_{1,5} = 19.38$; $P = 0.0035$). The x -axis is partialled for sex.

Fig. 4. Stereotypy correlates with a tendency to repeat previous responses (GLM: $F_{1,4} = 77.29$; $P = 0.0005$). The x -axis shows the number of trials taken to extinguish the previously learnt response, partialled for the number of trials taken to learn the original response (thereby controlling for motivational, perceptual or general learning differences), and sex.

During acquisition, correct choices were made faster than incorrect, while during extinction, animals reverted to choosing both arms of the maze with equal latencies. As predicted, stereotypy correlated with the number of trials taken to demonstrate equal choice latencies in both arms (GLM: $F_{1,4} = 14.48$; $P = 0.0095$), showing that in extinction, stereotypic animals persisted in responding rapidly to the previously-rewarded arm (Fig. 5).

As predicted, at the point where each vole was demonstrating complete knowledge by choosing both sides at chance, the most stereotypic animals displayed the smallest increases in their latencies to choose the previously rewarded side (GLM: $F_{1,4} = 42.91$; $P =$

Fig. 5. Stereotypy is correlated with a tendency to persist in responding rapidly to the previously rewarded side of the maze (GLM: $F_{1,4} = 14.48$; $P = 0.0095$). The x -axis shows the number of trials taken to choose both sides of the maze with an equal latency, corrected for sex and the number of trials taken to choose the correct side of the maze with a shorter latency during initial acquisition.

Fig. 6. Stereotypy correlates with evidence of knowledge-action dissociation (GLM: $F_{1,4} = 42.91$; $P = 0.0015$). In extinction, high stereotypy animals show a smaller increase in their latency to choose the previously rewarded side of the maze (i.e. their apparent knowledge) at the point where they are choosing at chance (i.e. showing by their choices that they 'understand' the task). The x -axis is partialled for sex, and the increase in latency to choose the previously unrewarded side of the maze (to control for individual differences, and changes in motivation).

0.0015) (Fig. 6), thus demonstrating the greatest discrepancies between their two behavioural signs of knowledge.

3.4. Activity

Unfortunately, one male and one female died prior to this final experiment. Nevertheless, as predicted, home cage activity levels were positively correlated with stereotypy (GLM: $F_{1,3} = 12.25$; $P = 0.0195$).

3.5. Intercorrelation of measures

The final, acid test of our hypothesis is whether all these measures inter-correlate. As predicted, all were positively correlated (Table 1). Indeed factor analysis of these data was not possible as all measures were so strongly correlated, implying that all these measures share a single common mechanism.

4. Discussion

To date, the understanding of clinical and experimentally-induced stereotypies has been little used to inform research on cage stereotypies [25,58]. Our study is thus the first to show a fundamental similarity between cage stereotypies and behaviours arising from basal ganglia dysfunction. As predicted, the bar-mouthing of caged voles correlated with the perseveration of response choices and short response latencies in extinction;

Table 1
Intercorrelation of the signs of altered basal ganglia function in bank voles

	Activity	Rate of initiation	Repetition of choices	Repetition of latencies	Knowledge–action dissociation
Stereotypy	$r = 0.857$ ($P = 0.0195$)	$r = 0.840$ ($P = 0.0035$)	$r = 0.642$ ($P = 0.0005$)	$r = 0.751$ ($P = 0.0095$)	$r = 0.790$ ($P = 0.0015$)
Activity		$r = 0.871$ ($P = 0.020$)	$r = 0.791$ ($P = 0.030$)	$r = 0.878$ ($P = 0.007$)	$r = 0.883$ ($P = 0.020$)
Rate of initiation			$r = 0.556$ ($P = 0.015$)	$r = 0.840$ ($P = 0.008$)	$r = 0.926$ ($P = 0.0005$)
Repetition of choices				$r = 0.772$ ($P = 0.0145$)	$r = 0.830$ ($P = 0.0105$)
Repetition of latencies					$r = 0.820$ ($P = 0.017$)

Correlation coefficients (r) between each combination of measures, and their significance (P), are listed. Correlation coefficients are partialled for sex and other covariates where specified in the methods.

evidence of a knowledge-action dissociation; enhanced rates of initiation of all behaviours; and greater baseline activity levels. Furthermore, all these signs were tightly intercorrelated, implicating a single underlying deficit consistent with a striatal disinhibition of response selection.

The profound differences seen between high and low stereotypy animals in this study (e.g. an order of magnitude difference in extinction performance and rates of behavioural switching), together with the fact that environmental treatments which affect cage stereotypy [45] also impact brain development, extinction learning, and the disinhibition of responses [48,61], argue that the suite of intercorrelated signs reported here reflects a differential impact of the captive environment upon these animals.

Previous accounts of rodent bar-mouthing, focussing on its motivational basis, have shown that it derives from attempts to escape the cage [49,77]. By showing that it is part of a suite of signs of altered behavioural control, our results now account for the persistence of this escape-behaviour. They also raise the possibility that central deficits are involved in many of the cage stereotypes so common in laboratory, zoo and agricultural animals. This finding has both ethical and practical implications.

Cage stereotypes are generally considered an animal welfare issue [44,58]. Such ethical concerns will be increased by this evidence suggesting that caging causes striatal dysfunction. Furthermore, our evidence of knowledge-action dissociation raises the possibility that stereotypic animals, like some human clinical patients [39,67], might feel frustrated by their impaired ability to turn decisions and preferences into actions.

Cage stereotypes could also potentially have some research value. Powell et al. [58] suggest that a mouse model of spontaneous stereotypy would be valuable for investigating the neural mechanisms of human clinical stereotypes, and our results support this suggestion. Our results also parallel other peculiar phenomena associated with stereotypy in clinical populations; for

instance, the enhanced rates of switching between behaviours seen in high stereotypy animals may parallel the disorganisation syndrome of schizophrenia, lending support to the hypothesis that disorganised symptoms may reflect striatal disinhibition in these patients [17]. Our results also resemble findings that in institutionalised Down's Syndrome patients, stereotypes are linked with an increased frequency of other behaviours [22], and the importance of physical or social environments for the development of cage stereotypy could thus perhaps help us understand the potentially deleterious effects of institutionalisation. For instance, ethological techniques have been useful in identifying physical and social features which elicit stereotypy in autistic children [30]. However, and perhaps more importantly, our results also raise questions about the way caged rodents are currently used in research.

Rodent models are essential research tools for neurobiology and the pharmacology and genetics of behaviour (e.g. [16]), but as reviewed in the Section 1, such rodents commonly display stereotypes in standard laboratory conditions. If stereotypers are dysfunctional, this has obvious implications for external validity [72,73]: it suggests that rodents with stereotypes are unlikely to be good models of normal functioning, or to provide normal backgrounds (reviewed in: [26]) for genetic or pharmacological manipulations. Furthermore, the frequency of cage stereotypy differs greatly between individuals, between sites, and between mouse strains; and the magnitude of strain differences in stereotypy also varies with husbandry (see [10,50,75]). Thus cage stereotypes represent an enormously variable, and currently uncontrolled—for, potential confound. This may well account for some strain and site effects on research results. For example, the behavioural disinhibition of stereotypers is particularly likely to affect any behaviour-based test involving locomotor activity, Open Field behaviour, reactivity to novelty, or extinction/reversal learning. Laboratory differences in cage stereotypy may therefore help predict and explain laboratory

differences in the results of standard behavioural tests [15].

Overall, we therefore suggest that husbandry techniques promoting low cage stereotypy—such as later weaning, [75], and suitable environmental enrichments [14,50,58,74]—will enhance the validity and replicability of laboratory rodent behavioural data, as well as improving caged rodents' welfare.

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