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Chapter 4

ANALYSIS OF ABNORMAL REPETITIVE BEHAVIORS IN EXPERIMENTAL ANIMAL MODELS

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ABSTRACT

Commonly observed in laboratory rodents, abnormal repetitive behaviors are an important domain for biomedical research. The neurological abnormalities associated with some behavioral perseverations and stereotypies in animals are similar to human brain disorders (for example, trichotillomania and obsessive-compulsive spectrum disorders), suggesting that micro-behavioral analysis of these phenotypes may benefit research in biological psychiatry. Additionally, expression of such phenotypes is highly sensitive to genetic manipulations, as well as environmental, social, husbandry, and other stressors. In this chapter we will discuss some specific rodent behavioral perseverations and stereotypies, their environmental modifiers, as well as potential translational value of these animal phenotypes.

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1. INTRODUCTION: ABNORMAL REPETITIVE BEHAVIORS (ARB)

Abnormal repetitive behaviors (ARB) have recently become appreciated in biomedical research, as these phenotypes are displayed in laboratory animals, and could possibly affect the reliability of behavioral and physiological data [1-3]. ARB are defined by the presence of perseverated actions that can be further classified according to the nature of the action performed and the particular components of behavior involved [4]:

1. Recurrent perseveration - repetitive motor behavior that serves no adaptive purpose, no proximate function, and has no cognitive input;
2. Stuck-in-set perseveration - repetitive goal-directed behavior that has no adaptive purpose but does effectively alter the environment; and
3. Limbic perseveration – repetitive behavior that results from cognitive abnormalities.

Typically, ARB are referred to as behavioral perseverations (BP) in the literature, and each of these classifications of perseveration result in a unique phenotype [1, 4].

BP are dysfunctional, repetitively performed behaviors, frequently exhibited by laboratory rodents [5], and can continue even with the removal of a stimulus [6]. BP can be divided into three distinct categories: 1) recurrence of a preceding response to a successive stimulus; 2) abnormal maintenance of a category of activity, or; 3) atypical prolongation of an activity [7]. It has been suggested that BP have no stress-reducing effects or adaptive benefits to the animals that perform them [5], however, they are not necessarily excessive in repetition [8]. Of particular interest, some BP phenotypes are sensitive to genetic, physiological and environmental manipulations, and may provide a simple yet high-throughput assessment of neurophysiological abnormalities in rodents with high translatability to human brain disorders [5].

Stereotypies are maladaptive behaviors, in that ordinarily normal animals cannot functionally cope when presented with stressors. For example, the induction of an animal into an abnormal environment (e.g., captivity) frequently results in stereotypic behaviors [1]. Although both BP and stereotypies involve repetitive or ritualistic behaviors, stereotypies (e.g., bar-mouthing, wire-gnawing, cage-top twirling, repetitive jumping, somersaulting, cage-lid climbing, and corner digging) can also be distinguished by their purposelessness [9], representing non-goal oriented or automatic persistence in mechanical repetition [1, 6, 10]. Furthermore, many stereotypies observed in captive laboratory animals are considered "recurrent perseverations," due to this apparent lack of function (e.g., do not raise fitness or alter the environment) [4]. Notably, these behaviors may confound laboratory research, as stereotypies can be mistaken for symptoms of disorder or disease. Although stereotypical behavior is considered a sign of psychological distress in animals, it can generally be reduced or eliminated through environmental changes [5, 11].

While both BP and stereotypies (and other ARB) are observed in animals kept in captivity, they differ in several other definable ways. For example, although both categories result in altered neurophysiology, as well as a reduced capacity to alternate between tasks, BP are thought to be caused by innate cognitive inflexibility [12], whereas stereotypies develop in response to the environment [5]. The cognitive inflexibility characteristic of BP is thought to be due to the disturbed neuroanatomical formation during development in captivity [1]. Additionally, BP are primarily associated with abnormal neurophysiology of prefrontal cortical structures [12], whereas stereotypies in particular may be linked to disturbed development of the striatum and the corticostriatal pathway [5].

Here, we will discuss the potential factors that contribute to ARB spectrum phenotypes in animals, as well as methods for their assessment, and the application of research findings to related neuropsychiatric disorders. We will specifically focus on barbering as an exemplary phenotype involving behavioral traits and physiological mechanisms typical for many ARB.

2. Experimental and Genetic Animal Models of ARB

Animal models are an important tool in biological psychiatry research, allowing the testing of etiological and physiological theories of brain disorders [2]. Behavioral models became particularly useful for the neurobiological mechanisms of BP and stereotypies. For example, tail chasing, weaving, fur chewing, excessive grooming, cleaning, pecking, food restriction-induced hyperactivity, reward alternation, excessive lever pressing, and marble burying, can all be categorized as naturally occurring repetitive behaviors [2]. Other examples of such repetitive behaviors in animals include excessive or inappropriate water-drinking, attack behaviors, territorial displays, chewing, vocalizations, pacing, freezing, foraging, nest-building, or wheel-running [13].

Environmental conditions are highly relevant to development of BP in many species, including mice, rats, non-human primates, and other mammals [5, 14]. For example, environmental enrichment reduces frequency of these behaviors, such as barbering [5], jumping, and backward flipping [10, 15, 16]. Furthermore, physiological markers are associated with the prevention of stereotypic phenotypes and include: reduction of abnormal neurological development and function in the corticostriatal loop [5], as well as increase of metabolic activity in the cortex and striatum [16], and higher levels of brain derived neurotrophic factor (BDNF) in the striatum [10]. The use of environmental enrichment to reduce the severity of neurological symptoms and the frequency of stereotypic phenotypes suggests that this model may help determine the neurological pathology that manifests ARB.

It is also important to note that there are several alternate experimental methods of inducing behavioral perseverations in animals. In one study by Bruto et. al (1984), acute administration of a neuroepinephrine neurotoxin (DSP4), provoked stereotyped behavior (e.g., excessive grooming, circling, gnawing) in the Y-maze task. Likewise, the deer mouse model of spontaneous and persistent stereotypy assesses the neurobiological factors associated with the expression of stereotypic hindlimb jumping [17]. Studies implementing the cortico-basal ganglia circuitry test the cognitive processes also mediated by this network. For example, environmental enrichment of deer mice attenuated repetitive vertical jumping and backward somersaulting, as well as ameliorated procedural and reversal learning in

contrast to standard housed counterparts [18]. Therefore, experience related to attenuation of stereotypic behaviors is associated with improved striatally-mediated learning and cognitive flexibility.

Genetic disposition also modulates the frequency and severity of ARB [5], also see Figure 1. In line with this notion, inbred C58/J mice also demonstrate stereotypic hyperactivity, repeated jumping, and back-flipping, in addition to lack of sociability and poor learning acquisition [19]. This aberrant stereotyped behavior occurred in the home cage (e.g. using wire lid to perform back-flips), social test box, and the T-maze. Remarkably similar to deer mouse stereotypy, these repetitive motor responses in C58/J mice may be reduced through environmental enrichment, and standard housing conditions may have contributed to the high levels of spontaneous stereotypic behaviors [19].

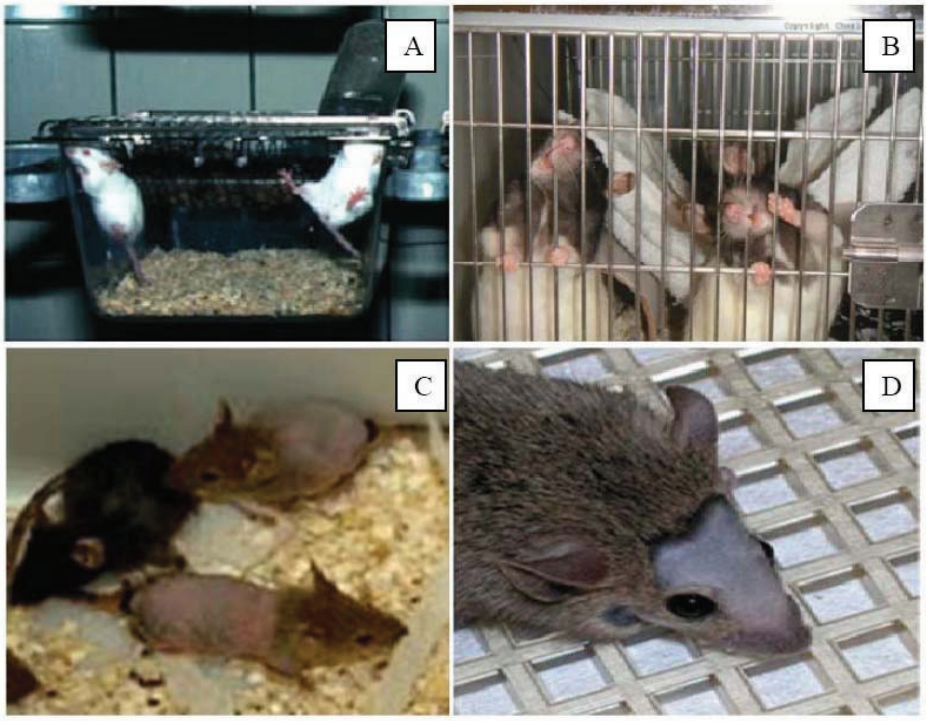

Figure 1. Examples of abnormal repetitive behavior (ARB) phenotypes in rodents. A – bar-mouthing and jumping in mice; B – bar biting in rats, C, D – excessive barbering in mice. Photos A-C: www.aps.uoguelph.ca/~gmason/StereotypicAnimalBehaviour/library.shtml, with permission; Photo D: courtesy of B. Dufour and J. Garner).

In addition to the increased tendency of certain strains to display repetitive behavior, strains utilizing specific gene knockouts have also been shown to affect these phenotypes. Thus, sensitivity of behavioral perseverations to genetic manipulation may prove integral in modeling similar neuropsychiatric disorders. Several examples illustrate this point particularly well.

M_2 muscarine acetylcholine receptor knockout (KO) mice show marked impairment in set-shifting in the Barnes circular maze task, returning to the starting hole significantly more than control, implicating increased perseverative behavior [20]. BP have been suggested to be strongly correlated with deficits in set-shifting [5], which is also referred to in the literature as behavioral inflexibility [20]. Recent findings suggest that this characteristic reduction in behavioral flexibility may be associated with abnormal function of the prefrontal cortex and basal ganglia [5, 20], and possibly in the hippocampus [20].

In another study [21], using Ts65Dn mice, a mouse model for Down syndrome, researchers found that this particular strain elicited significant increases in repetitive jumping and repetitive cage-top twirling compared to control mice. Using a battery of tests (e.g., acoustic startle response, accelerating rotor rod), this study showed that additional environmental stressors did not increase frequency of stereotypy, suggesting a stronger influence of genetic factors for these stereotypic behaviors [21].

One recent study attempted to develop a mouse model of OCD by comparing the rigid syntactic structure of mouse grooming patterning to the similarly rigid sequential BP observed in OCD patients. A mutant mouse strain was developed by genetically removing the dopamine transporter (DAT), resulting in an elevated level of extracellular dopamine in the neostriatum. These DAT KO mice showed higher resistance to disruption during grooming sequences, supporting the influence of the dopaminergic system on behavioral inflexibility. Thus, hyper-dopaminergic mutant mice may be a useful model in further elucidating the neurophysiological abnormalities associated with BP in OCD [22].

3. RODENT BARBERING AS A TYPICAL EXAMPLE OF ARB

3.1. Biological Rationale

Barbering (see figure 1) represents a behavioral phenotype observed in many species, and is particularly common among laboratory mice. Representing a behavior-associated hair loss, it is also referred to as whisker-eating, whisker trimming, hair nibbling, hair pulling, behavior-associated alopecia areata, and the Dalila effect [23-26]. Although rodent barbering has been reported frequently throughout the literature, there is still little known about how or why this behavior occurs [3, 5].

Barbering is defined as an animal's removal of hair from itself (self-barbering) or its cage-mates (hetero-barbering). Hetero-barbering involves a situation when an individual plucks or trims fur and/or whiskers from cage-mates on the nose, head, shoulders, forearms, or elsewhere [3, 23, 26-28].

The patterns of alopecia formed during barbering are typically similar for the barber's cage-mates, and this pattern is referred to as the barber's "cutting style" [26]. Cutting styles may also differ between mouse strains, as some strains tend to pluck whiskers from the face, while others pluck their idiosyncratic pattern from any area that is accessible [3, 26, 27], also see figure 1.

There is a growing interest in rodent barbering, both as a husbandry problem [24, 29] and as a phenotype for translational biopsychiatry research [3, 27, 28]. Additionally, there is an increasing number of mutant and transgenic laboratory mouse strains with robustly affected

barbering phenotypes (see table 1). Of particular interest, barbering is associated with risk factors (e.g., genetic and environmental, stress) and neurological abnormalities similar to some obsessive-compulsive spectrum disorders in humans [5]. Collectively, this indicates that the quantitative and qualitative assessment of barbering may ultimately give insight into similar human brain disorders [5].

Table 1. Examples of barbering phenotypes in genetically modified mice (data obtained from Mouse Genome Informatics and PubMed, 2008)

Model	Background Strain	Phenotype	References
Phospholipase C beta1 knockout mice	F1 C57Bl/6J(N8) x129S4/SvJae(N8)	Lack of whisker trimming	[50]
Complexin II knockout mice	F1, F2 129Ola x C57BlV6	Lack of whisker trimming	[51]
Transgenic mice over-expressing G protein-coupled receptor 85	C57BL/6	Reduced whisker trimming	[52]
Vitamin D receptor knockout mice	129S1	Reduced whisker trimming and fur barbering	[53]
Transcription factor USF1 knockout mice	C57BL/6	Increased whisker trimming	[54]
Aromatase knockout mice	C57BL6J x J129	Increased whisker trimming and fur barbering	[28]

There have been several theories proposed to explain why barbering occurs in experimental rodents. The *dominance hypothesis* [3, 25] explains barbering as a function of a social hierarchy within a group of animals, as it is typically observed that one dominant individual remains unbarbered. According to this theory, barbering behaviors may be adaptive insofar as establishing and maintaining a social hierarchy, and may reduce aggression and improve survival of the animals. Further validating this concept, cage-mates seem to voluntarily participate in barbering, and it negatively correlates with aggression [3, 26]. Another argument in favor of this theory comes from our observation on sexually experienced NMRI male mice, which were put together (e.g., 4 mice per cage). Following 2-3 days of extensive fighting, the social hierarchy was established, fighting stopped, and all mice but one were severely barbered (Kalueff 2005, unpublished observations).

The *coping hypothesis* attempts to explain barbering as an adaptation to unnatural or inadequate housing, or in captivity [30, 31]. In general, behavioral perseverations, of which barbering is one robust example, are seen to have no adaptive value insofar as improving the fitness of an organism in response to its ever changing environment [5, 32]. It is likely, however, that whisker plucking in mice may result in reduced dendritic density in the barrel cortex [26], disrupting sensory function vital to mouse survival [5], and possibly affecting thermoregulation [5, 33]. Although coping functionally reduces stress in response to an adverse situation, there is no evidence supporting the hypothesis that barbering has a stress-reducing effect for the barbers [5]. Indeed, through measuring the blood-corticosterone levels in of Zur:ICR mice, Würbel and Stauffacher (1996) found that prevention of a similar BP (e.g. wire gnawing) did not cause a long-term increase in corticosterone concentration. This perseveration was replaced by increased activity in the cage. However, despite an initial increase in corticosterone, they found that 72 hours after treatment, levels had returned to

baseline [34]. This evidence suggests that stereotypies may not aid the individual in reducing chronic stress.

Another theory tends to explain barbering phenotype as a pathological behavior that is exaggerated in response to poor environmental conditions. The *pathology hypothesis* asserts that abnormal brain function is strongly associated with barbering behavior. Additionally, this hypothesis explains that barbering has no adaptive value to the animals, and should be considered to be dysfunctional in nature as it is a consequence of abnormal brain development rather than an adaptation to the environment [5]. In line with this, the unnatural environment in which laboratory mice develop has been shown to alter brain structure and function [5]. In mice raised in isolation, self-barbering [5] as well as other stereotypies [35] have been seen to occur with alarming frequency. Thus, it is likely that barbering may be influenced by disturbed neuro-anatomical development, and consequently, the abnormal function of dopaminergic (e.g., the prefrontal corticostriatal) [5, 35, 36], and possibly serotonergic pathways [2, 5, 35]. Additionally, certain abnormalities in the anatomy and physiology of the prefrontal cortex and striatum may also be involved [5].

While the exact biological reasons for barbering remain unclear, many studies indicate that it has a strong genetic component, as barbering occurs more frequently in some mouse strains than others (figure 1), and because some genetic manipulations may robustly affect barbering phenotypes (table 1). Thus, the *genetic hypothesis* of barbering may also provide important insights for further research in this field. In support of this hypothesis, prevalence varies between mouse strains. For example, Balb/c strains rarely barber, in contrast to most 129 strains which express barbering behavior with approximately 50% incidence [3, 5]. In addition, some strains, such as NMRI mice, may express this behavior with up to 100% incidence [3]. Although there is an apparent influence of genetic components on barbering, it likely is not dependent on a single gene or allele [37]. Indeed, this idea is supported by the fact that barbering does not occur with equivalent frequency between populations that are inbred for generations, and thus are genetically identical [5, 27].

Finally, it is possible that barbering represents a more *complex*, *multifactorial* phenomenon, and several different context-specific factors (rather than a single rationale) play a role in this behavior [3].

3.2. Barbering as an ARB-Like Phenotype Associated with Brain Disturbances and Environmental/Husbandry Stress

Several lines of evidence indirectly support the value of barbering in studying brain pathology. For example, neurobiological abnormalities in the striatum, prefrontal cortex, and the corticostriatal pathway are seen in both rodent barbering and human trichotillomania, an obsessive-compulsive spectrum disorder (OCSD) [5]. Behavioral perseverations similar to barbering, such as bar-mouthing (See figure 1A), have been linked to the basal ganglia [32], which is of particular interest here as ablation of the basal ganglia has been observed to decrease an individual's capacity to regulate symptoms of trichotillomania [38]. Additionally, both barbering and OCSD are behaviors that involve repetitive goal-directed behavior, decreased set-shifting, interrupt social interaction, and are performed excessively [5]. Set-shifting refers to an organism's capacity to alternate between goal-directed behaviors [39, 40], and is associated with the prefrontal cortex [36, 41, 42], and the basal ganglia [43, 44].

Deficits in set-shifting have been suggested to result from corticostriatal pathway disruption [45, 46], and is often seen in patients with trichotillomania [47]. It is also important to note that both of these behaviors can be considered to be maladaptive, as they result from disturbed neurophysiology largely due to abnormal developmental conditions [5].

Although biological and genetic differences (e.g., table 1) influence the frequency of barbering behavior in rodents, it is clear that these effects are exacerbated by environmental stress, such as living in an unnatural (e.g., laboratory) environment [5]. This concept has been supported by the fact that barren cage conditions have been shown to cause abnormal behavior, such as stereotypies [48]. Other husbandry factors may also contribute to increased frequency of barbering, such as being housed in metal cages, caged with siblings, or in isolation [5, 24]. Weaning mice before they are old enough or when they are a low weight has also been shown to increase incidence of barbering [48]. Isolation rearing also adversely effects neuroanatomical development, particularly in the prefrontal cortex and striatum, and consequently alters physiology of this dopaminergic system [35, 36].

Interestingly, enriching the environment to reduce barbering in mice or non-human primates may have parallels with trichotillomania in humans. For example, environmental enrichment may mitigate mouse barbering behavior by reducing stressful factors as well as relieving boredom [5], while human hair plucking behavior (similar to animal barbering) is also increased by stress or boredom [5, 49]. The similarities in neurological and environmental factors, as well as the parity of resulting behavior, suggest that barbering (like many other BP) may be useful in investigating neuropsychiatric pathology, such as trichotillomania and other OCSD [5]. It is important to note, however, that barbering does not involve diminishment of affective shifting, whereas OCD is a combination of deficits to set-shifting as well as affective shifting [4]. Therefore, the interpretation of results from a barbering model may give insight into one component of OCSD symptoms. Further research is required to fully substantiate a comprehensive animal model for OCD.

4. CONCLUSION

While the complex differences between ARB further scientific exploration, the neurobiological pathways and structures associated with these phenotypes reveal insight into these common laboratory behaviors. Despite strong genetic contributors to perseverative behaviors in animals, improved environment (i.e., proper husbandry, environmental enrichment) has been shown to decrease some of these symptoms [14, 24, 29], and therefore must be considered seriously in the context of this book. In both animals and humans, it is important to note the synergy between their repetitive-like behaviors, and poor, unnatural environmental conditions [5, 27]. In order to address this aspect, one must consider animal perseverations as a complex phenotype, based on many factors, such as: genetic components (e.g., mouse strain, genetic manipulations), environmental stressors afflicting the individuals, the resulting neuro-anatomical abnormalities, and the social microcosms of animal colonies. Further investigation is needed to focus more specifically on animal ARB-like phenotypes, and their applicability to human psychiatric disorders as well as to animal stress research, basic neuroscience, and bioethics.

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