# Barbering (Fur and Whisker Trimming) by Laboratory Mice as a Model of Human Trichotillomania and Obsessive-Compulsive Spectrum Disorders

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Animal diseases that develop spontaneously in a limited subpopulation can provide powerful models of human disease because they provide a means to investigate the interaction of a broad range of biological and environmental etiologic processes. In contrast, with experimentally induced animal models, the etiology of the model is inherently fixed, and can only speak to a limited subset of those involved in the human disease. 'Barbering' (abnormal whisker- and fur-plucking behavior) in mice resembles human trichotillomania (compulsive hair plucking) in that barbering mice pluck focused areas of hair, and engage in post-plucking manipulatory and oral behaviors. We performed a cross-sectional epidemiologic survey of a population of 2,950 laboratory mice to further assess the face validity of barbering as a spontaneous model of trichotillomania. Patterns of hair loss and demographic and etiologic risk factors were recorded for each mouse, and were analyzed by use of logistic regression. Barbering paralleled trichotillomania in terms of phenomenology, demography, and etiology. Thus, similar to trichotillomania, barbers predominately plucked hair from the scalp and around the eyes and the genitals; barbering was female biased, and had its onset during puberty; and etiologic factors included reproductive status and genetic background. Therefore, barbering has excellent face validity as a model of trichotillomania, and may represent a refined and non-invasive model, especially for studies of the complex genetic/environmental etiologies of this disorder.

Many animal models of human mental disorder share a common limitation; unlike the human disorder—and unlike many animal models of somatic human disorders, such as diabetes mellitus (1)—clinical signs of disease manifested by the model do not develop spontaneously, but instead are experimentally induced. This is true of well established animals models, such as isolation-rearing and amphetamine models of schizophrenia and learned helplessness models of depression (51), as well as more recent models, such as the Borna disease virus model of autism (41) and the 8-Hydroxy-2-(di-n-propylamino)-tetralin hydrobromide (8-OH-DPAT) model of obsessive-compulsive disorder (OCD) (12). Consequentially the etiology of the model is necessarily different from that of the disease in many human patients. In contrast, spontaneous animal models allow explicit investigation of etiology. For instance, the responses of different mouse strains can be compared to investigate genetic influences on drug addiction (10).

Spontaneous abnormal behaviors are common in confined animals (14, 19, 35). Barbering, for example, is a common abnormal behavior in laboratory mice (27, 43), where barbers (i.e., mice performing the behavior) pluck hair from their companions, leaving idiosyncratic patterns of baldness (Fig. 1).

We suggest that barbering by mice may represent a model of compulsive hair-pulling behavior in trichotillomania in particular, and obsessive-compulsive spectrum disorders (OCSD) in general, that could offer unique insights precisely because it develops



**Figure 1.** Example of barbering. The whiskers and much of the fur have been removed from this mouse by its cage mate.

spontaneously in laboratory mice. A crucial first step in critically validating any such suggested model is to assess its face validity (i.e., whether the behavior in animals has the same phenomenology, demography, and etiology as the human disorder) (51). This is a process that is distinct from assessing 'construct validity' (whether the same underlying processes are involved) and predictive validity (whether treatments in humans can be predicted from the model, and vice versa) (51). We therefore review previous studies to assess existing evidence that speaks for and

against the face validity of barbering as a model of trichotillomania and other OCSD, and to identify key questions that remain unanswered. We then present data that address these outstanding issues.

The phenomenologies of trichotillomania and barbering are similar. Thus, trichotillomania sufferers repeatedly pluck hair from idiosyncratic body locations, in particular the scalp, the eyebrows and eyelashes, and the pubic region (8). Although most plucking is self directed, sufferers will also pluck other individuals (8); upholstery (2); pets (i.e. contraspecifics [21, 50]); and dolls (47), where the patterns of hair loss mimic those of the sufferer. Unfortunately, to our knowledge, there are no published quantitative data on the exact proportion of patients that pluck other individuals. Once plucked hair is manipulated, often orally, by most patients (8).

Similar to hair-plucking in trichotillomania, hair is removed in idiosyncratic repeated patterns by barbers. In a typical cage of barbered mice, all but one individual will have near-identical patterns of hair loss. The intact individual (the 'barber') is removing hair from its companions. The whiskers are usually removed, and may represent the only site of hair loss (22, 27, 36, 43, 46, 49). Sometimes overlapping patterns of barbering on all individuals are observed, and these can be attributed to two barbers at work in the same cage (18, 27). Barbers hold down their cage mates and remove hair by plucking with their incisors. Once removed, the hair is often chewed by the barber (43). Barbering mice housed with contraspecifics (e.g., rats) will also remove hair from them (22).

Two key phenomenologic differences between barbering and trichotillomania are, therefore, apparent. Barbers pluck orally, whereas trichotillomania sufferers pluck manually. This difference may merely reflect the differing biology of the species: mice principally groom and manipulate objects with their teeth, whereas humans principally groom and manipulate objects with their hands. Although trichotillomania sufferers self-pluck, self-barbering has not yet been observed. Additionally, it is unclear whether there are phenomenologic similarities or differences in terms of body areas barbered or plucked.

Virtually nothing is known of the demography of barbering. In contrast, trichotillomania is well characterized. It is strongly female biased (e.g., 92.5% of patients [7]), although it has been suggested that this difference may merely reflect a sex difference in the proportion of sufferers who seek help (8). Nevertheless, sex differences are also apparent in the lifetime prevalences observed in college freshmen (9): 1.5% in males, and 3.4% in females (2.5% overall). Trichotillomania generally has its onset during or immediately after puberty (7), but may begin at any age (7, 8).

Epidemiologic studies provide essential insights into potential causes, especially in human populations. Thus, the cause of trichotillomania may involve a genetic component; familial studies suggest that there are increased rates of trichotillomania and other comorbid disorders among relatives of trichotillomania patients (8). Hormonal factors may also play a role. In female patients, trichotillomania symptoms may worsen premenstrually or during pregnancy (24); pregnancy is also associated with the onset or worsening of symptoms in patients with OCD (28, 30). The onset of trichotillomania is also often associated with environmental stressors (8), especially social stress, such as parental divorce (50). In studies investigating social risk factors, adult trichotillomania sufferers experienced a greater severity of physical abuse and emotional neglect as children than did controls

(26), and 86% of sufferers experienced one or more episodes of physical, emotional, or sexual abuse or violence in the year preceding the onset of the disorder (compared with approximately 1% of the general population) (5). Finally, there is a report of trichotillomania being imitated, or otherwise spreading through a population of patients in close contact (8).

Various similar etiologic factors have also been proposed for barbering behavior. There are anecdotal reports of strain differences (22, 27), suggesting genetic influence on the behavior. It has also been suggested that breeding mice are more likely to barber, but data to this effect do not exist. Environmental stressors, such as barren environments (11), transparent cage design, and exposed cage position (18), and social stressors, such as early weaning (38) and being housed with siblings (18), also affect the behavior. The relationship of barbering to normal grooming and allogrooming behaviors is unknown. Early weaning could play a role similar to the putative role of childhood abuse or neglect in the development of trichotillomania. Contrary to popular belief, barbering is not a dominance behavior, as it is equally common in dominant and subordinate mice (18). Furthermore, the presence of a barber in the cage encourages, rather than suppresses, barbering behavior in cagemates. Thus, like trichotillomania, barbering appears to be socially transmitted or facilitated (18).

Given these unanswered issues, certain predictions can be made to objectively test the face validity of barbering as a model of trichotillomania. We therefore performed a large-scale study to empirically assess the phenomenology and epidemiology of barbering. (The role of husbandry effects and social factors are described in detail elsewhere [18]). To further assess phenomenologic similarities between barbering and trichotillomania, we looked for evidence of self-barbering in singly and group-housed mice, and collected detailed data on the areas of hair loss. To further assess demography, we predicted that barbering would be more common in females than males; that barbering would become increasingly common with age; and that barbering would have its onset after puberty. To further assess etiology we predicted that barbering would be affected by strain (i.e., genetics) and by breeding status.

## Methods

**Data collection and processing.** Data were collected using a cross-sectional epidemiologic survey design. The population studied comprised all mice housed in our Small Animal Facility (five rooms). This technique provides a cross sectional 'snapshot' of a population, and allows the relationship between the response (barber or non-barber) and potential risk-factors to be ascertained (3, 32, 33, 52). Each, room, rack, and cage in the facility was surveyed, in turn, between April 2000 and June 2001.

Every mouse was visually inspected on the dorsal and ventral surfaces. A patch of missing fur was scored as evidence of barbering if: the exposed skin was non-puritic (i.e., the exposed skin was neither red nor inflamed); there was no scarring or scabbing around the patch of missing fur; the mouse was otherwise in good health, and the fur where present was in good condition; another cause for the missing fur could not be ascertained (for detailed methods see 18). No skin problems were diagnosed in the colony, and mice did not manifest signs of inflammation or reddening of the skin.

Patterns of hair loss on each mouse that were due to barbering were drawn by four experimenters on a standardized 'mouse map' (Fig. 2). These experimenters were trained to draw maps
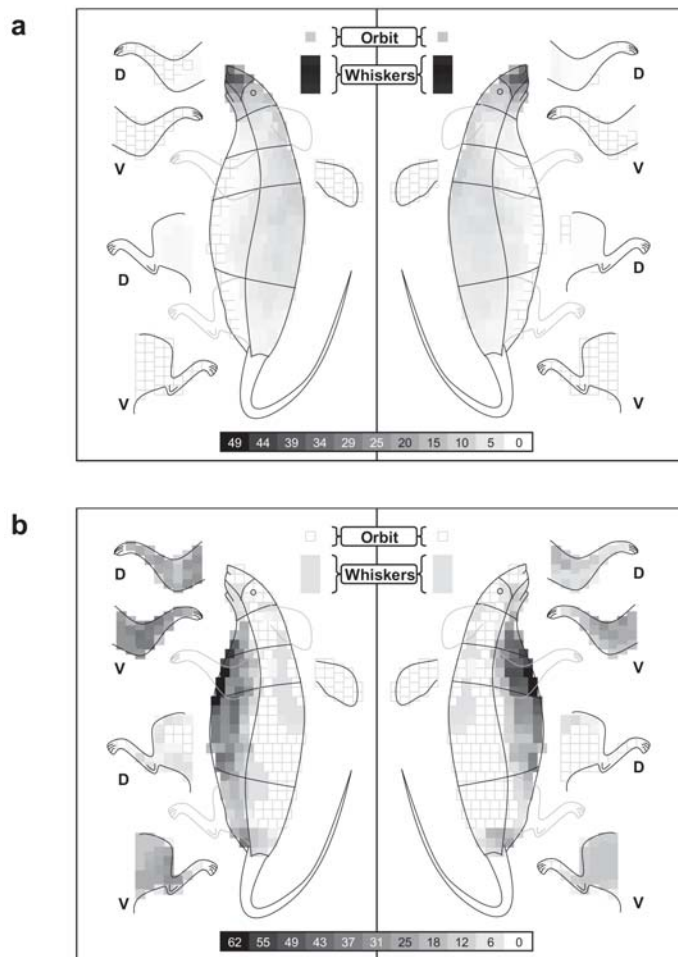
**Figure 2.** 'Mouse maps' showing the mean severity of barbering (i.e., mean % of area denuded) over the entire body, for: (a) cagemate-barbers, and (b) self-barbers. Notice the different scale bars for the two figures. In cages where a self-barber was pair-housed with another barber, the assigning of some map squares to either mouse was equivocal; hence (for example), the very slight barbering of the whiskers seen in the self-barbers. White squares with no border have trace amounts of hair loss. White squares with a gray border have 0% hair loss. The positions of the limbs and ears are indicated on the map of the body itself for illustrative purposes only; the map squares on the body correspond to those body areas that lie underneath the limbs and ears. Map squares for recording hair loss on the ears, and the dorsal (D) and ventral (V) views (rather than surfaces) of the limbs are depicted adjacent to the body. These views correspond to the areas of the limb visible from above when the mouse is free to move (D), and from the underside when the mouse is handled (V).

that were consistent with those drawn by one of the authors (JPG). To aid consistency, the 'mouse map' marks key anatomical reference points (e.g. the midline, and anterior and posterior limits of the shoulder) (Fig. 2). These drawings were then entered into a custom-written database by a single author (BD). This software deduced the patterns of hair loss due to each barber, and calculated barbering severity scores for each barber (i.e., mean proportion (%) of skin denuded) for the entire body, and for separate body areas (Fig. 3). (The software is available from the authors on request [for a detailed description of this software, see 18]). A wide range of biological, environmental, and husbandry factors were recorded for each mouse. All data were recorded directly into a second custom-written database that was linked
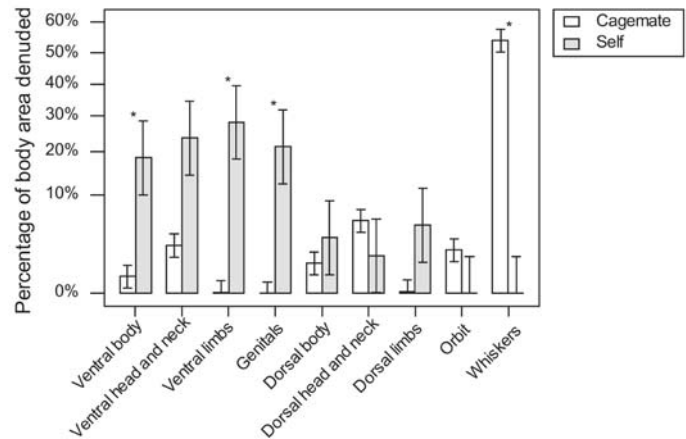


**Figure 3.** Statistical comparison of the pattern of hair removed by cagemate-barbers versus self-barbers. Body areas that differed significantly in severity of barbering between the two types of barber are marked with (*). The body areas listed here correspond to the areas delineated by the black 'guidelines' on the 'mouse map.' The dorsal rump, back, and shoulder regions on the map were summed to give the 'dorsal body' region. The groin area was subdivided into squares mapping the genitals, and those mapping the groin. These latter squares were added to the belly and thoracic regions on the map and were summed to give the 'ventral body' region. The dorsal views of the fore and hind limbs on the map were summed to give the 'dorsal limbs' region, and the ventral views of the fore and hind limbs to give the 'ventral' limbs region.

with the database containing the observed patterns of hair loss. For transgenic, knock-out, or knock-in mice, or inbred sub-strains, the background strain was designated, to maximize the sample size within each genetic grouping (i.e., background strain; Table 1). Whether the background strain was inbred or outbred was also coded.

**Identifying self-barbers.** We found five singly housed mice in the data set that had missing fur on the ventral body surface. These mice must have been self-barbers. We then re-examined the data for mice with this unusual pattern of missing ventral fur, and for cages where the patterns of fur loss were inconsistent with cagemate-barbering (a cagemate barber will barber all the mice in the cage in a similar pattern). We found a further 12 group-housed mice with similar patterns of missing fur on the ventral region of the body. Five of these were pair housed and were the only barbered mouse in the cage, and therefore must have been self-barbers (two of these mice had incomplete data and, so, were excluded from further statistical analysis, though their data were included with those of Fig. 2B). Three were housed in larger groups with a cagemate-barber, and were the only mice in the cage with ventral fur loss, so they must have self-barbered their ventral fur. Four were housed with one other mouse that also was barbered; thus, it was not possible to uniquely attribute their ventral hair loss to these four mice (these mice were excluded from statistical analyses and from the data in Fig. 2B).

**Subjects and housing.** Due to the nature of the study, we surveyed mice already housed and in use by other investigators (total of 2,950 mice). Additional mice were not bred for the study. The study was performed under the existing IACUC general husbandry protocols for the Small Animal Facility. Similarly, the nature of an epidemiologic study requires existing variation in the factors under investigation, and controls for other sources of variation. Therefore, differences in housing conditions (e.g., stock-

**Table 1.** Total number of mice included in the analysis (N), and cagemate-barbering odds ratios for the various background strains in the study

| Inbred? | Background strain | N | Odds ratio | 95% CI for odds ratio | | P (odds ratio) |
|---|---|---|---|---|---|---|
| Inbred | C57BL/6J-[+]/A[y] | 13 | 76.62 | 4.29 | 1368.17 | 0.003 |
| Inbred | 04 | 48 | 24.28 | 1.51 | 389.41 | 0.024 |
| Inbred | C57BL/6J | 309 | 14.12 | 1.70 | 117.04 | 0.014 |
| Inbred | FVB | 132 | 1.66 | 0.12 | 22.70 | 0.705 |
| Inbred | Ju | 40 | 1.47 | 0.05 | 43.89 | 0.824 |
| Inbred | A/J | 24 | 0.00 | 0.00 | - | 0.998 |
| Inbred | CBA | 105 | 1.00 | | (Reference level) | |
| Outbred | 04 x CD1 | 138 | 25.38 | 4.35 | 147.99 | < 0.0005 |
| Outbred | CCX | 774 | 4.32 | 1.24 | 15.04 | 0.021 |
| Outbred | CD1 | 376 | 1.00 | | (Reference level) | |
| | All inbred strains | | 0.46 | 0.05 | 4.40 | 0.503 |
| | All outbred strains | | 1.00 | | (Reference level) | |

The odds for barbering for each background strain is divided by the odds for barbering of a reference background strain. For ease of comparison, the background strain with the lowest non-zero odds of barbering was chosen as the reference level. Thus, CBA was the reference background strain for inbred mice, and CD1 was the reference level for outbred mice. As odds ratios are calculated separately within inbred and outbred background strains, the overall odds ratio of inbred to outbred background strains also is given. Thus, for instance, C57BL/6J mice are 14.12 times more likely to barber than CBA mice (*P* = 0.014). The C57BL/6J-[+]/A[y] mice are C57BL/6J mice heterozygous at the agouti locus: one allele ([+]) is the C57BL/6J agouti wild-type, the other is the A[y] allele, which confers a bright yellow coat color. Background strain 04 is an exotic strain maintained at UC Davis, inbred from an original cross of BALB/c, C57Bl/6J, C3H, and DBA mice. The CCX mice are an outbred cross of CBA and C57Bl/6J mice.

ing density, cage type) were recorded, quantified, and included as controlling factors in the analysis. Breeders were fed Purina LabDiet 5015 (3), and stock mice were fed Purina LabDiet (Purina, St. Louis, Mo.) 5008. Most mice in the study were bred at the facility. The Rodent Health Surveillance Program in the facility calls for screening sentinel animals from each room on a quarterly basis. Examination includes histologic, parasitologic, microbiological, and serologic examinations. Opportunistic *Staphylococcus* infections were not detected during the course of the study. Ectoparasites have never been detected in the facility. *Actinobacillus* sp. is endemic in all rooms in the study; mouse hepatitis virus is endemic in two of five rooms; and *Klebsiella* sp. is endemic in two of five rooms. Skin problems were not diagnosed in any colony member, nor were any infections that might lead to hair loss.

**Exclusion criteria.** We first excluded any mice for which we could not unequivocally ascertain patterns of hair loss or risk factors of interest. Thus, unweaned pups were excluded from the analysis since the husbandry protocols in some rooms precluded their handling (n = 937), as were mice involved in surgical procedures where the fur was shaved (n = 36). One-thousand nine hundred seventy-nine mice passed these initial criteria. We observed four cages where a self-barber also appeared to be barbering its cagemate; however, in these instances, it was not possible to unequivocally assign areas of hair loss to these self- and cagemate-barbers as all were pair-housed. These four mice were, therefore, excluded from further analysis, leaving 1,975 mice. Finally, we removed five additional mice (two of which were self-barbers) for which we could not record all the data required for statistical analysis, leaving data for 1,970 mice available for analysis.

**General analytic methods.** Barbering status (non-barber or barber) was investigated using logistic regression (Minitab 12 for Windows, Minitab Inc., State College, Pa.). Barbering severity was investigated using the mixed-model general linear models (GLM) procedure (SAS 8 for Windows, SAS Institute Inc., Cary, N.C.). Both of these methods allow blocking factors, and explicitly investigate the effect of each independent variable controlling for the effects of all others. Thus, the lack of matching inherent in a design of this sort is controlled for statistically.

Of the 11 self-barbers that passed the exclusion criteria, all but one were found in the same room; all of the self-barbers in this room were of the same background strain (CCX—an outbred cross of strains CBA and C57BL/6J). Therefore, all statistical analyses involving self-barbers were limited to CCX mice from this room (68 cagemate-barbers, and 10 self-barbers).

Suitable transformations were applied to the data to meet the assumptions of GLM (normality of error; homogeneity of variance; and linearity), which were confirmed post-hoc. Model fit for logistic regression was assessed, using Pearson, Deviance, and Hosmer-Lemeshow goodness-of-fit tests, and Somers' D, Goodman-Kruskal's Gamma, and Kendall's Tau as measures of association.

**Body areas and barber types.** To investigate whether particular body areas were favored for barbering, and whether the body areas selected varied between self- and cagemate-barbers, the severity scores for each body area were compared using a mixed-model analysis of variance (ANOVA). Body areas could be either ventral or dorsal; thus, body area was nested within these body regions. The interactions of body area * barber type and dorsal versus ventral * barber type were investigated. Significant effects were investigated by use of Bonferroni-corrected planned contrasts. The analysis was blocked by mouse nested within sex and barber type. Severity scores were angular transformed.

**Risk factors for barbering.** Risk factors for cagemate-barbering were examined separately from those of self-barbers because of the confounding of self barbers with room and background strain. Due to the small number of self-barbers and the resulting strong confounding of potential risk factors, risk factors for self-barbering could not be determined. Risk factors were examined using logistic regression. The analysis was done using Logit, Normit, and Gompit link functions, and results were compared for model fit. Model fit was similar under all link functions. Logit was, therefore, adopted to allow the calculation of odds ratios (52). The odds of an event is the probability of it occurring divided by the probability of it not occurring; thus, an odds of 3:1 corresponds to 75% probability of the event occurring. Odds ratios describe the relative likelihood of an event under two different circumstances.

Of the 1,970 mice available for this analysis, we first removed the 11 self-barbers remaining in the data set, leaving a total of 1,959 for the analyses described in this section (the numbers given later for each variable in the analysis are for just these 1,959 mice). For cagemate-barbering, the analysis was blocked by
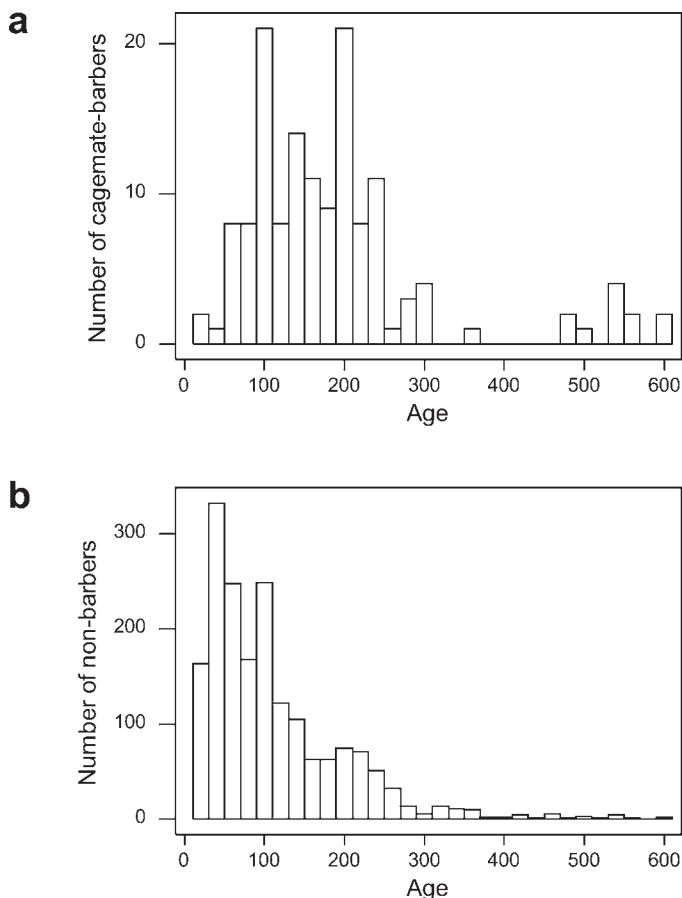
a



b



**Figure 4.** Age distribution of (a) cagemate-barbers, and (b) non-barbers.
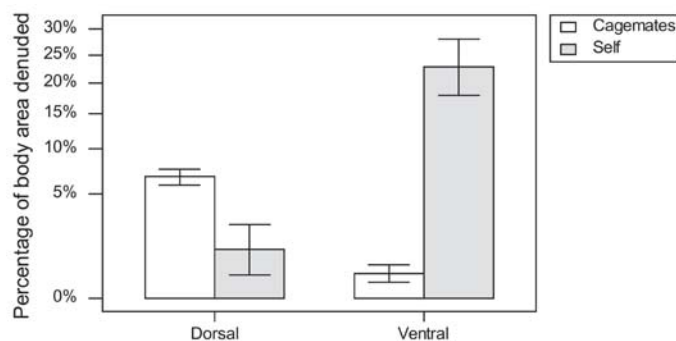


**Figure 5.** Overall severity of barbering on dorsal and ventral regions. Post-hoc test results indicated that cagemate- versus self-barbers differed significantly in severity of barbering of dorsal and ventral regions. The severity of barbering of dorsal versus ventral regions was significantly different for both types of barber.

room; cagemate relationships (siblings [1,542] vs. non-siblings [322], vs. mixed [95]); cage type (clear plastic cages with perforated steel tops and automatic water [991], or steel bar tops and water bottles [30] vs. steel with slotted steel tops and water bottles [938]); cage height from floor; cage horizontal position (whether the cage was on the side or the middle of a rack); stocking density (76.1 to 12.7 square inches per weaned mouse); and the number of adults in the cage (one to 12 weaned mice per cage). These blocking factors were included because they represented husbandry factors likely to affect barbering, and we wanted to control for any effect that they might have. Minimum room temperature over the month prior to data collection in a room varied from 19°C to 21°C, maximum temperature from 22°C to 25°C, minimum relative humidity from 41 to 50%, and maximum relative humidity from 65 to 94%. The number of mice housed in a room that were included in the analysis varied from 185 to 779.

The analysis included the effects of: age (21 to 595 days, Fig. 4), background strain (Table 1); inbreeding (Table 1); sex (male [837] vs. female [1,122]); and breeding status (breeders [536] vs. same-sex stock mice [1,423]). The breeding status * sex interaction was examined, then was removed from the model as it was not statistically significant. Age effects were further investigated, using a GLM procedure with the same model terms, except that age was now the dependent variable, and barbering was an independent variable. Age was logarithmically transformed.

**Barbering severity in cagemate-barbers.** Factors affecting the severity score for cagemate-barbers were examined, using the GLM procedure. The same factors and model were used as those used in the logistic regression analysis. Severity scores were logarithmically transformed. Severity scores for self-barbers were not examined due to the small sample size.

## Results

**Prevalence.** Of all mice surveyed, 1,979 passed the initial exclusion criteria for the analysis. Four (0.2%) mice appeared to barber themselves and their cage-mates, and were excluded from further analysis (see Methods). One-hundred forty-two (7.2%) mice barbered their cagemates. Of the 13 mice (0.7%) that unequivocally self-barbered, five were singly housed, representing 5.7% of the 88 singly housed mice in the sample.

**Body areas and barber types.** Figure 2 depicts the average barbering severity for cagemate-barbers and self-barbers on the 'mouse map,' including data from the two self-barbers excluded from further analysis. Barbering severity on different body areas indicated marked differences between cagemate-barbers and self-barbers (body area * barber type interaction: $F_{7,518} = 7.88$; $P < 0.0005$; Fig. 3). Post-hoc tests indicated that the genitals, ventral surface of the body, and ventral views of the limbs were more severely denuded by self-barbers, and that the whiskers were more severely denuded by cagemate-barbers. The two types of barber also denuded dorsal and ventral body surfaces overall differently ($F_{1,518} = 70.56$; $P < 0.0005$; Fig. 5). The overall barbering severity in self-barbers was 8.8% of body area denuded versus 2.5% in cagemate-barbers.

**Risk factors for, and severity of cagemate-barbering.** For cagemate-barbering, significant risk factors were: age (odds ratio = 1.01; z = 8.50; $P < 0.0005$); background strain ($\chi^2$-test = 37.012; $df = 8$; $P < 0.0005$), sex (male:female odds ratio = 0.64; z = –2.17; $P = 0.030$); and breeding status (non-breeding:breeding odds ratio = 0.18; z = –4.72; $P < 0.0005$). Interestingly, despite the marked difference between background strains (Table 1), inbred background strains did not differ from outbred background strains overall (z = –0.67; $P = 0.503$). Females were approximately one-and-a-half times more likely to barber than males. Once corrected for all other factors, breeders were approximately five times more likely to barber than stock mice. For instance, for female CCX mice aged 100 to 150 days, three of 10 (30%) of the breeders barbered, and nine of 82 (11%) of the stock mice barbered.

Once all other factors were controlled for, the odds of being a barber increased by a factor of 1.01 with every day of age (or 1.07 with every week). The mean age of barbers was 139 days (95% confidence interval [CI]: 124–156) versus 89 days (95% CI: 84–95) for non barbers (GLM: $F_{1,1935} = 74.50$; $P < 0.0005$) (Fig. 4). The mean age of breeders was 153 days versus 81 days for stock animals (GLM: $F_{1,1935} = 175.33$; $P < 0.0005$). The youngest barbers observed were 22 days old; however, these two mice could possibly have been barbered by a parent, as both were barbered in a similar pattern. The next youngest barber observed was 50 days of age, and was unequivocally a barber. The prevalence of barbering increased steadily with age, from 1.4% at 20 to 60 (mean, 40) days of age (puberty); to 7.0% at 100 days; 14.0% at 140 days (mean age of barbers); leveling off at 19.9% at 200 days; and reaching 21.4% at 300 days. None of the factors significantly affected severity of barbering.

## Discussion

**Barbering as a model: face validity.** In the introductory section, we compared key features of the phenomenology, demography, and etiology of trichotillomania and barbering. From these comparisons, we predicted features of barbering that would provide an objective assessment of the face validity of barbering as a model of trichotillomania. These results clearly support the face validity of barbering as a model of trichotillomania. The prevalence of the behavior was somewhat higher than that of trichotillomania. However this difference may merely reflect the relative barrenness of, and/or stressors unique to the laboratory mouse's environment.

In addition to the phenomenologic similarities discussed previously, these data indicate that there are additional similarities between barbering and trichotillomania. Most importantly, we observed a number of self-barbering individuals, eliminating the major phenomenologic distinction between barbering and trichotillomania. Three possible reasons spring to mind for the failure to report self-barbering in earlier literature. Self-barbering might have been overlooked or attributed to cagemates since barbering is defined de facto as the removal of hair from other mice. Also, the concentration of self-barbering on the ventral body surfaces, and away from the whiskers, might have led to self-barbering going unnoticed (mouse defensive postures make it difficult to observe the ventral body surface during routine husbandry), or to such hair loss being attributed to other causes. Finally, self-barbering might occur almost exclusively in singly housed mice, and thus, be similarly overlooked, especially as all studies to date have examined only group-housed mice. Self-plucking is common in mammalian (15) and avian (34) species, and human trichotillomania often involves a similar mixture of self-plucking and other-plucking behaviors by the same individual (2, 8). The relative scarcity of self-barbers versus cagemate barbers may reflect the relative scarcity of singly housed mice, as self-barbers were often singly housed individuals. This, in turn, suggests that the balance of self- versus other-plucking associated with trichotillomania may, in part, reflect the social isolation that the disorder can engender, the inhibition of the behavior in social situations (8), and the (presumably) extreme social consequences of plucking other humans. The plucking of other individuals (whether they be humans, pets, dolls, or other inanimate objects) by trichotillomania sufferers may, therefore, deserve further attention.

Two key differences between mouse and human plucking aid in interpreting the barbering patterns observed: mice have a far greater range of body sites from which to pluck; and mice pluck orally, whereas humans pluck manually. It is not surprising, therefore, that self-barbers do not barber the whiskers, orbit, or dorsal head regions. In addition, the defensive posture adopted by barbered mice (43) prevents cagemate-barbers from reaching the ventral body surface, the genitals, and much of the limb area. Within these limitations, it is striking that the orbital areas, the dorsal head region, and the genitals are favored sites for barbering (Fig. 2), just as they are favored sites for plucking by trichotillomania sufferers (8).

The whiskers (of cagemate-barbers) and the ventral surface of the neck and body and ventral views of the limbs (of self-barbers) also were strongly favored. These areas are rarely plucked by trichotillomania sufferers, but this is not surprising, as they also are non-hirsute areas of the human body. Thus, in sum, barbering has many phenomenologic similarities to those of trichotillomania.

Demographic similarities, in terms of sex and age, also were apparent. Thus, females were one and a half times more likely to barber than males (controlling for all other variables). Although this is less marked than the odds ratio of 2.55 for humans calculated from the data of Christenson and co-workers (9), this result nonetheless parallels the sex bias reported for trichotillomania and OCD. Although the basis for sex differences is unclear, in mice at least, it cannot be due to differences in reporting frequency (8), or social or cultural differences, as has been proposed for several other sex-biased human OCSD (31).

Barbering became increasingly common with age. Puberty and sexual maturity are essentially coincident in mice, and although age at sexual maturity varies by strain, most mice reach puberty/sexual maturity between 34 and 56 days of age (45). Therefore, as predicted, the youngest unequivocal barber was pubescent. The prevalence of barbering then increased to an asymptote of approximately 20% by 180 days of age. Thus, as predicted, the demography of barbering matches that of trichotillomania in terms of sex bias and prevalence with age.

Turning to etiology, there was evidence for a role of genetics and breeding status. Thus, marked background strain differences in barbering were evident. Of the background strains widely housed in other laboratories, C57BL/6J mice were the most likely to barber (e.g., 13.5% of individuals versus 1.3% of CD1 mice). Background strain differences in barbering also indicated a number of fascinating genetic effects. Notably, C57BL/6J-+/A^y mice were approximately five and a half times as likely to barber as C57BL/6J mice (i.e., C57BL/6J-+/+), although there was an insufficient sample size of C57BL/6J-+/A^y mice to assess the significance of this difference. The C57BL/6J-+/A^y mice are genetically identical to C57Bl/6J mice, except that they carry a single A^y allele at the agouti locus. This allele codes for a complex pleiotropic phenotype (23, 44), including bright orange coat; obesity; and alterations in dopamine, norepinephrine, and serotonin metabolism. This locus, however, is clearly not the only one affecting barbering behavior, as evidenced by the prevalence of barbering in two other crosses commonly seen in the colony. Background strain CCX is an outbred cross of CBA and C57BL/6J mice, and has a prevalence of barbering almost exactly midway between that of the parental background strains. In contrast, when background strain 04 is crossed with CD1 mice, the prevalence of barbering in the progeny is almost identical to that of the paren-

tal 04 background strain.

Parallelling trichotillomania and OCD, breeding mice were approximately five and a half times more likely to barber than non-breeders. Thus, trichotillomania may be associated with reproductive events: symptoms often worsen during the premenstrual period; and may be exacerbated by pregnancy (24). This pattern fits well with OCD, where 19 to 25% of female sufferers experience onset during the last trimester or immediately after parturition (28, 30); 73% of existing sufferers experience a worsening of symptoms during the same period (30). These effects have been related to the role of oxytocin in the reproductive cycle, which interestingly also regulates grooming behavior in rodents. However, the lack of a significant sex * breeding status interaction indicates that there was no significant difference between the sexes in the effect of breeding status on barbering.

Although breeding status was predicted to affect barbering in females, the result in males is more surprising. Reproductive males may be more likely to barber than non-reproductive males due to the many potential social stressors surrounding reproduction; for instance, male house mice take part in parental care and offspring defense, and the close proximity and odor of other reproductive pairs would signal a serious threat to the offspring in the wild (25). Alternatively, the presence of the female, or her behavior may play a role. Thus, the female may, in some way, represent a stressor to the male (pregnant female mice can become aggressive), or barbering behavior might in some way be derived from courtship, mating, or parental behavior. We are unaware of any data on the impact of reproductive events on trichotillomania in human males.

Thus, as predicted, potential etiologies for barbering include genetics and reproductive status, parallelling epidemiologically identified potential etiologies for trichotillomania. However, unlike humans where such studies are impossible, controlled follow-up studies in mice provide the possibility of confirming or elucidating the causal connections between epidemiologically identified potential etiologies and final outcomes.

**Barbering as a model: application and insights.** Barbering, therefore, appears to have excellent face validity as a model of trichotillomania. Additionally, the application of barbering as a model of trichotillomania and OCSD presents several advantages over existing or proposed models, and thus may represent a major refinement in the modeling of these disorders.

Barbering is not experimentally induced. This contrasts, for instance, with the 8-OH-DPAT model of OCD, where repetitive behavior is induced acutely using a serotonin 5-hydroxytryptamine $(5HT)_{1A}$ receptor agonist (12); or the D1CT model of OCD, where dopamine $D_1$ receptors are potentiated with a cholera toxin transgene (6). These models are examples of induced models that do not pertain to a known human etiology (i.e., human OCD is a chronic disorder, not an acute drug-induced state, nor is it the result of genetically engineered dopamine receptors), but are instead guided by hypothetical mechanisms in the human disorder. Such experimentally induced models are limited in their validity to instances of the human disorder that do share a common mechanism.

Barbering is not limited in construct validity (i.e., common disease processes) to a specific etiology. This contrasts, for instance, with infection of neonatal rats with a Borna disease virus as a model of autism (41). Such models attempt to induce a known human etiology in the animals, and therefore only have strong va-

lidity for similar etiologic subpopulations of the human disorder. Given the complex gene/environment interactions underlying most human disorders, this constraint seriously limits the efficacy of such induced models. Although laboratory housing is arguably itself a treatment, the fundamental difference is that barbering develops spontaneously from a range of etiologic factors in a subset of laboratory mice. Hence, barbering can provide unique insights into the full range of genetic and environmental etiologic factors in humans.

Many other spontaneous models of trichotillomania or OCSD, are of poor overall face, construct, and predictive validity (e.g., acral lick dermatitis [37]). This point is discussed in detail elsewhere (15, 20). For example, stereotypies (goal-less repeated patterns of identical motor output manifested by confined animals [29]), such as acral lick dermatitis, have convergent face and predictive validity to OCD (i.e., they share a non-specific resemblance) in that they are repetitive, and they respond to Selective Serotonergic Reuptake Inhibitors (SSRIs), respectively (37, 40). However stereotypies fail to have discriminant validity to OCD (i.e. stereotypies do not show the unique diagnostic criteria that discriminate behaviors in OCD from symptoms in other disorders). For instance, stereotypies and compulsive behaviors are considered to be two fundamentally different behavioral signs in human psychiatry (2, 20) (i.e., poor face validity); stereotypies and OCD involve fundamentally different brain mechanisms (20, 48) (i.e., poor construct validity); and stereotypies respond to drugs that fail to treat OCD (20) (i.e., poor predictive validity). In contrast, barbering is clearly not a stereotypy because the behavior is variable and goal directed (20, 43). As a result, barbering is the only spontaneous model of trichotillomania or OCSD where face validity has been empirically assessed. These examples emphasize the importance of assessing all forms of validity in a model, and assessing convergent and discriminant validity, particularly in spontaneous models.

Other proposed spontaneous models of trichotillomania or OCSD involve use of exotic (e.g., parrots [4]), large (e.g., dogs [37] or horses [39]), or long-lived (e.g., parrots) animals. Use of large and long-lived animals presents logistic problems, especially in a spontaneous model where a large number of animals may need to be bred. Use of exotic or long-lived animals also exacerbates the ethical problems with such research. These issues are minimized by using mice.

Finally, despite the possible welfare consequences of barbering itself (16, 43), the behavior may nonetheless provide a less invasive model of trichotillomania and OCSD by providing a refined model that can also reduce the number of mice used (c.f. 42). Thus, barbering animals can be selected from the pool of stock animals that exist in any sizeable breeding colony, or from retired breeders. Otherwise breeding sufficient mice to yield a study population of barbers is likely to involve production of excess asymptomatic mice. Compared with other experimental manipulations previously discussed, barbering not only pertains to a wider range of human etiologies, but also represents a non-invasive model. Research into barbering may also benefit the welfare of laboratory mice, and contribute to the treatment of similar behaviors in other animals.

Considering data from barbering mice provides a number of potential insights into trichotillomania and OCSD. Thus, the background strain effects seen here emphasize the role of genetics in the etiology of barbering, and the possible increased preva-

lence of barbering in C57BL/6J-$^+$/A$^y$ mice provides a tantalizing hint at a number of possible physiologic pathways. Most genetically modified mice are derived from C57BL/6J stock, which means there is a rich array of neurotransmitter and receptor knockout mice already available from this high-barbering background strain. These mice could aid the investigation of potential genetic and physiologic etiologies underlying trichotillomania and other OCSD.

The clear sex effects for barbering lend support to the argument that the female sex bias seen in trichotillomania reflects a strong underlying biological etiology, rather than being due to social etiologies or an artifact of reporting effects. Perhaps most importantly, the combined female sex bias, exacerbation by breeding, and postpubertal onset associated with barbering, all point to a central role of reproductive status. The potential roles of reproductive status and underlying hormones (especially oxytocin) therefore deserve further attention in trichotillomania and other OCSD, as does the further assessment of this relationship in male patients.

Several social and abiotic stressors appear to be risk factors for barbering (18), emphasizing the importance of the environment in the etiology of trichotillomania. Evidence for the social transmission or facilitation of barbering (18) supports the suggestion that similar etiologic mechanisms may exist in trichotillomania. It may be particularly fruitful, for instance, to examine the role of such effects in susceptible clinical populations, especially the potential role of factors, such as lack of environmental complexity or novelty, or lack of control over the physical or social environment, in institutionalized patients (*c.f.* 13, 17).

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