

## Identity domains in complex behavior: Toward a biology of personality

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## Abstract

1 Personality traits offer considerable insight into the biological basis of individual differences.  
2 However, existing approaches toward understanding personality across species rely on  
3 subjective criteria and limited sets of behavioral readouts, resulting in noisy and often  
4 inconsistent outcomes. Here, we introduce a mathematical framework for studying individual  
5 differences along dimensions with maximum consistency and discriminative power. We validate  
6 this framework in mice, using data from a system for high-throughput longitudinal monitoring of  
7 group-housed mice that yields a variety of readouts from all across an individual's behavioral  
8 repertoire. We describe a set of stable traits that capture variability in behavior and gene  
9 expression in the brain, allowing for better informed mechanistic investigations into the biology  
10 of individual differences.

## 11 **Introduction**

12 Individual differences are a hallmark of living organisms and central to our understanding of  
13 normal behavior and psychopathology. In humans, consistencies in emotional and behavioral  
14 expression have been extensively investigated and categorized by psychologists within the  
15 framework of personality traits<sup>1,2</sup>. In other species, however, the understanding of individual  
16 differences and the biological processes that underlie them has been hindered by the absence  
17 of a strong conceptual foundation behind the trait creation process and the lack of  
18 comprehensive behavioral screening paradigms.

19 Here we propose to resolve these issues using a computational framework for capturing and  
20 describing the space of individual behavioral expression by reducing diverse longitudinal  
21 behavioral data to trait-like dimensions. Personality traits can be thought of as having two crucial  
22 characteristics: (1) they capture and represent a continuous gradient of differences between  
23 individuals of the same species and (2) they tend to be stable for individuals over time. Thus, a  
24 mathematical formulation of a trait informed directly by these properties would be a dimension  
25 that captures the maximum behavioral variability between individuals while maintaining  
26 minimum variability within individuals over time. We use the term Identity Domains (IDs) to  
27 describe such traits obtained from decomposing a high-dimensional space of the measured  
28 behaviors. Conceptually similar to principal component analysis, which identifies the directions  
29 of maximum variability, our linear discriminant analysis (LDA) decomposition-based approach  
30 seeks the dimensions with maximal discriminative power and stability by maximizing the  
31 between- to within-individual variability ratio (Figure 1a). We validate this framework in mice, one  
32 of the most commonly used model organisms in neuroscience and psychiatry research, and a  
33 species that readily allows for exploration of the biological underpinnings of individual  
34 differences.

## 35 **Results**

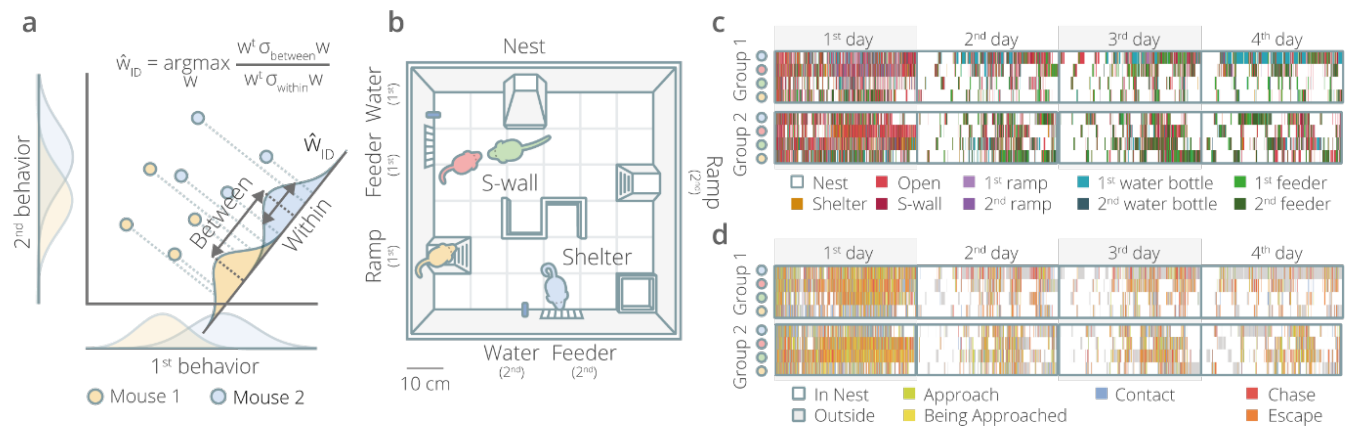
### 36 **The Social Box paradigm**

37 In order to assess the broadest variety of ethologically relevant voluntary mouse behaviors, we  
38 used a long-term “Social Box” living paradigm, wherein mice are housed in an enriched, semi-  
39 naturalistic environment in groups of four and monitored over multiple days<sup>3,4</sup> (Figure 1b-d,  
40 Supplementary Movie 1). Automatic location tracking of individuals allowed high-throughput  
41 behavioral data collection with readouts consisting of both individual (e.g., locomotion,  
42 exploration, foraging patterns) and social (e.g., approaches, contacts, chases) behaviors. A total  
43 of 60 features per mouse, per 12-hour active phase was collected (Supplementary Figure 1a). We  
44 initially monitored 42 groups of four outbred male mice (a total of 168 animals) left undisturbed  
45 over a period of at least four days.

### 46 **Linear Discriminant Analysis**

47 An initial analysis of the readouts from this dataset revealed a subset of behaviors that, in  
48 themselves, were discriminating between and/or stable within individuals (Supplementary Figure  
49 1b), suggesting that the Social Box paradigm could capture some of the information necessary  
50 for building IDs. We thus proceeded to train our algorithm on this dataset. Our analysis yielded  
51 four significant IDs that passed the threshold of less than 5% average overlap between  
52 individuals (Supplementary Figure 2, ID5 – the first dimension below this threshold is shown for  
53 comparison). The dimensions produced this way were uncorrelated, though not necessarily  
54 orthogonal, resulting in four IDs each spanning a very different behavioral subspace (Figure 2a).

55 To test the replicability of the four IDs, we used a separate dataset composed of control mouse  
56 measurements ( $n = 208$ ) in Social Boxes with a different layout (Supplementary Figure 3a), which  
57 yielded only a subset of the current behavioral readouts (37 different readouts per mouse per  
58 active phase). The scores on the top four IDs obtained from this dataset correlated strongly with  
59 the respective original scores (Supplementary Figure 3b). The strength of this relationship  
60 decreased steeply at ID5. We were thus able to replicate the initial ID structure on an independent  
61 dataset despite the differences in setup and readouts.

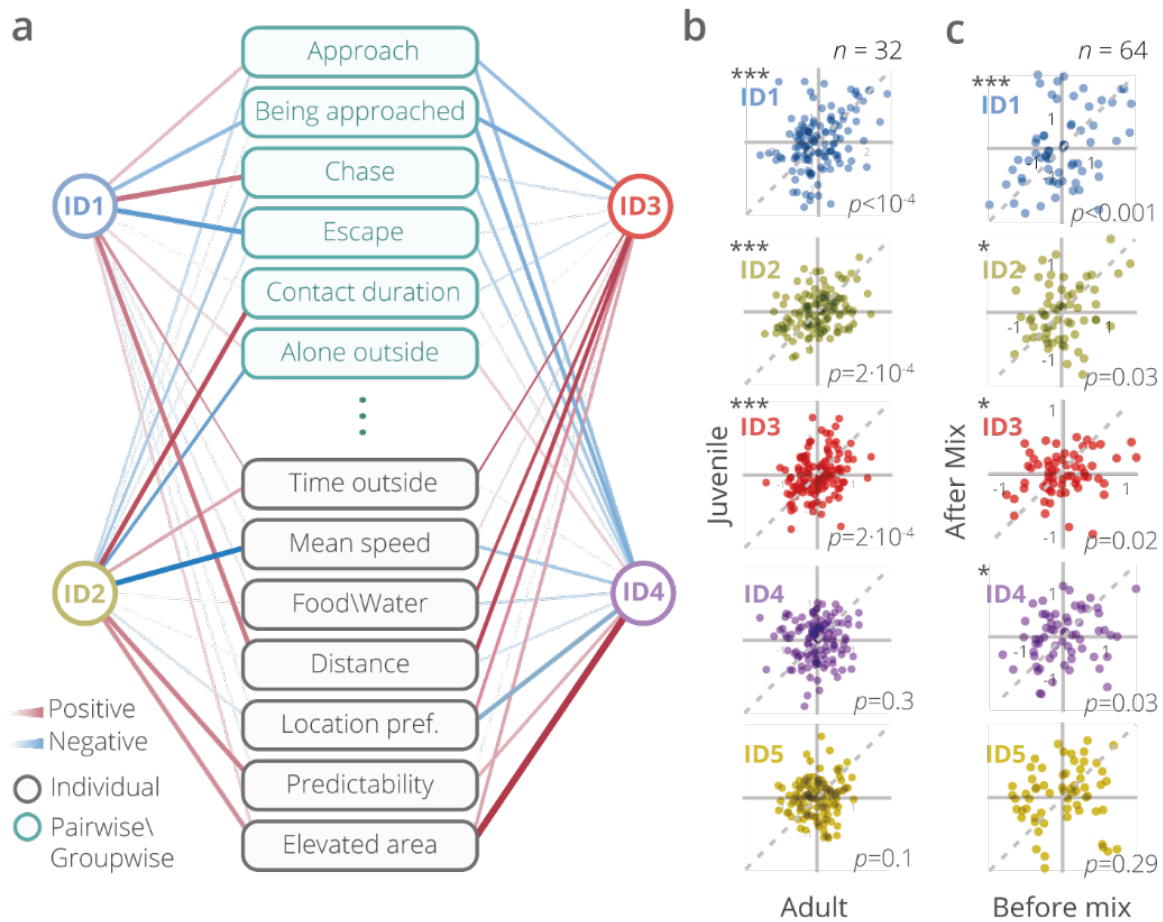


**Figure 1.** From behavior to personality. (a) The task of finding stable and discriminative trait-like dimensions can be formulated as an optimization problem. We used Linear discriminant analysis (LDA) to reduce the multidimensional behavioral space by creating dimensions that maximize the ratio of inter- to intra-subject variability. (b) Groups of four male mice, marked for tracking purposes with dyes of 4 different colors, were housed in an enriched environment where they could move and interact freely over multiple days. All of their movements were automatically tracked. Each arena contained a closed nest, 2 feeders, 2 water bottles, 2 ramps, an open shelter, and a S-shaped separation wall in the center. (c) Movement ethograms and (d) social ethograms for 2 representative groups of mice show intra-individual consistencies and inter-individual variability.

## 62 IDs are stable over time, developmental stages, and social context

63 Having established our model, we proceeded to experimentally validate the IDs. To assess the  
 64 stability of ID scores over time, we first tested their self-similarity from an average of the first four  
 65 days of the experimental period to the 5<sup>th</sup> day (Supplementary Figure 4). All IDs fulfilled this  
 66 criterion. We then tested their stability over developmental time, by assessing juvenile mice (8  
 67 groups, 4-5 weeks old) in the social arenas. The same mice were tested again as adults (15-16  
 68 weeks old). Individual scores on IDs 1-3 were stable over this prolonged period of time (Figure  
 69 2b, Supplementary Figure 5), indicating that IDs assigned to juveniles captured individual  
 70 differences that remained stable across developmental stages.

71 A major reason for the usefulness of behavioral traits over specific behaviors is that traits more  
 72 closely approximate the intrinsic properties of an individual and are therefore more robust



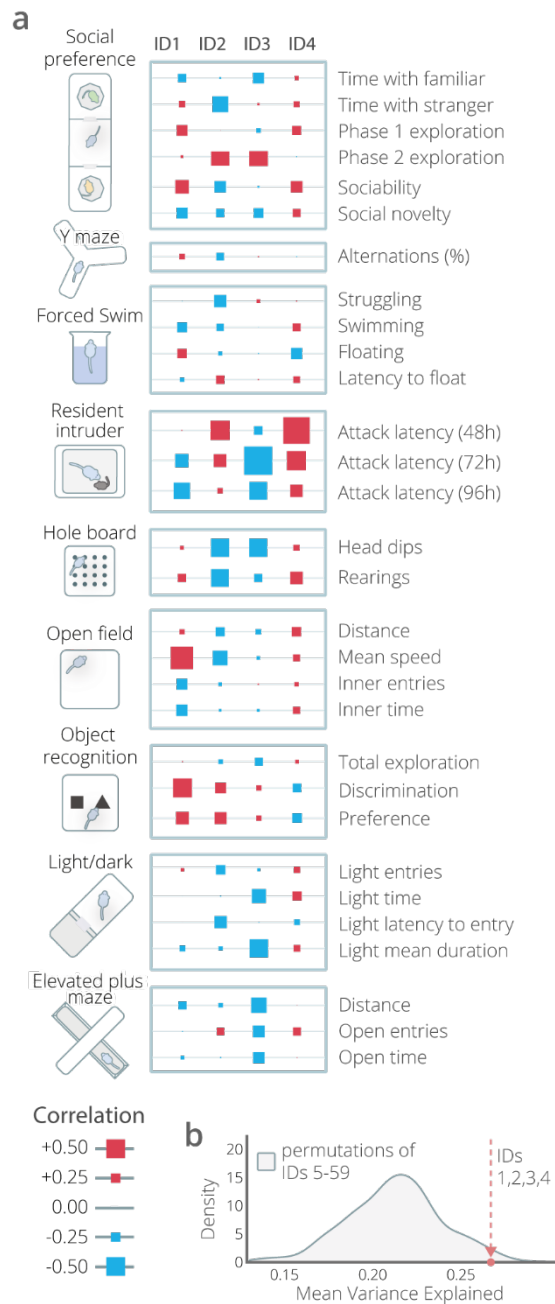
**Figure 2.** Testing the Identity Domains (IDs). (a) Running linear discriminant analysis (LDA) on the 60-dimensional behavioral space resulted in four significant IDs. The IDs are uncorrelated between themselves and are represented by multiple overlapping behaviors (showing 13 representative behaviors out of the 60, see **Supplementary** Figure 9). The width of connecting lines reflects the strength of the correlation (red – positive, blue – negative). (b) ID scores of mice as juveniles (4-5 weeks old) remained significantly stable at adulthood (15-16 weeks old) for the first three IDs. (c) ID scores of mice before and after being mixed into new social groups. Mice were significantly self-similar in their scores on IDs 1 through 4 across changing social environments. This relationship did not hold for ID5.

73 against manipulations of the social environment. Mice from 16 groups (64 individuals) that had  
 74 been assigned ID scores based on the four-day baseline testing were then shuffled into new

75 groups, such that no mouse had ever been exposed to any of its new group members and re-  
76 introduced to new arenas for another day of measurements (Supplementary Figure 6). For adult  
77 male mice, this is a dramatic and stressful manipulation causing significant changes in many of  
78 the behavioral readouts, especially those related to general locomotion and aggression. Despite  
79 these changes, the scores for IDs 1 through 4, but not ID5, remained significantly self-similar to  
80 their baseline state (Figure 2c). We additionally compared our model against PCA run on the same  
81 dataset. In this analysis only two out of the four top four principal components remain stable  
82 after this manipulation (Supplementary Figure 7a-c). Thus, mice tended to maintain the  
83 distinguishing individual characteristics captured by IDs despite substantial changes to the social  
84 environment.

#### 85 **IDs combine information from a variety of standard behavioral tests**

86 Having established that four IDs were stable over time and across social context, we set out to  
87 assess their ability to predict a range of standard behaviors typically measured in classical mouse  
88 behavioral paradigms. To this end, we submitted mice with known ID scores to a battery of  
89 established behavioral assays (Figure 3a-b). ID scores contained a significant portion of the  
90 information collected from classical tests (Figure 3a). The pattern of correlations between the  
91 various tests and ID scores additionally suggests that IDs represent complex entities that could  
92 not be fully captured without comprehensive behavioral screening. Moreover, these  
93 relationships contribute to the notion that IDs carry information about the hidden factors that  
94 are co-modulated across an animal's behavioral repertoire. For example, ID1 was correlated with  
95 a measure of dominance in the social hierarchy (David's score, Figure 5b) and also with features  
96 of locomotion in the open field test and memory recall in the object recognition test. All of these  
97 behavioral readouts appear to be expressions of a common underlying trait.

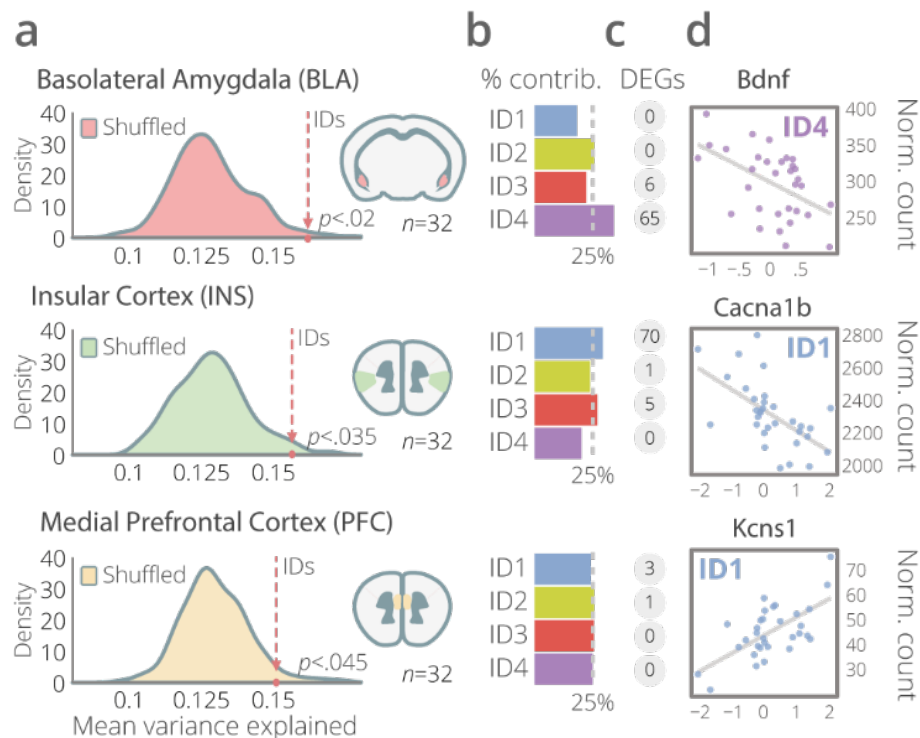


**Figure 3.** Identity Domains (IDs) are reflected in multiple standard behavioral tests. (a) ID scores predict multiple readouts across standard tests (two-tailed Pearson correlation statistic). Moreover, some standard test readouts are related to multiple IDs. The strength of each correlation is represented by the size of the squares (red – positive, blue – negative). (b) Variance explained by ID scores in standard behavioral assays. IDs 1-4 explain significantly more variance in “classical” behavioral test readouts than random sets of 4 from IDs 5-59.



## 98 **IDs capture transcriptomic variance in the brain**

99 A major advantage of animal models is the ability to mechanistically investigate the link between  
100 brain and behavior. While the contributions of brain-transcriptomic differences to human  
101 personality traits remain largely unexplored due to major technical difficulties in performing such  
102 studies, mouse ID scores may prove a useful proxy. To assess whether ID scores captured  
103 transcriptomic variance in the brain, we performed bulk RNA-sequencing in mice that had been  
104 profiled in the Social Box (n = 32). For each individual, we sequenced three brain regions (Figure  
105 4): the basolateral amygdala (BLA), the insular cortex (INS), and the medial prefrontal cortex (PFC),  
106 yielding a total list of 13,073 genes jointly detectable in all three regions. For each region, we  
107 assessed the average variance explained across the gene set by all four IDs and compared it  
108 against a distribution derived from shuffling the ID scores across individuals. Strikingly, in all  
109 three regions, the IDs performed significantly better in their true configuration than would be  
110 expected by chance, suggesting that ID score assignment is close to optimal with regard to their  
111 association with gene expression.



**Figure 4.** Identity Domains (IDs) carry information on gene expression in the brain. (a) RNA-sequencing results from the basolateral amygdala, insular, and medial prefrontal cortices of mice collected after baseline behavioral assessment. Plotted are the distributions of mean R-squared values for 200 models with four shuffled IDs as predictors. ID scores explain significant amounts of variance in the transcriptome (permutation test). (b) The relative contributions of each ID to the transcriptomic variance explained in each region. (c) Numbers of genes showing differential expression per ID after multiple testing correction. (d) Expression of one representative gene from each region plotted against individual scores on the ID with which it was associated.

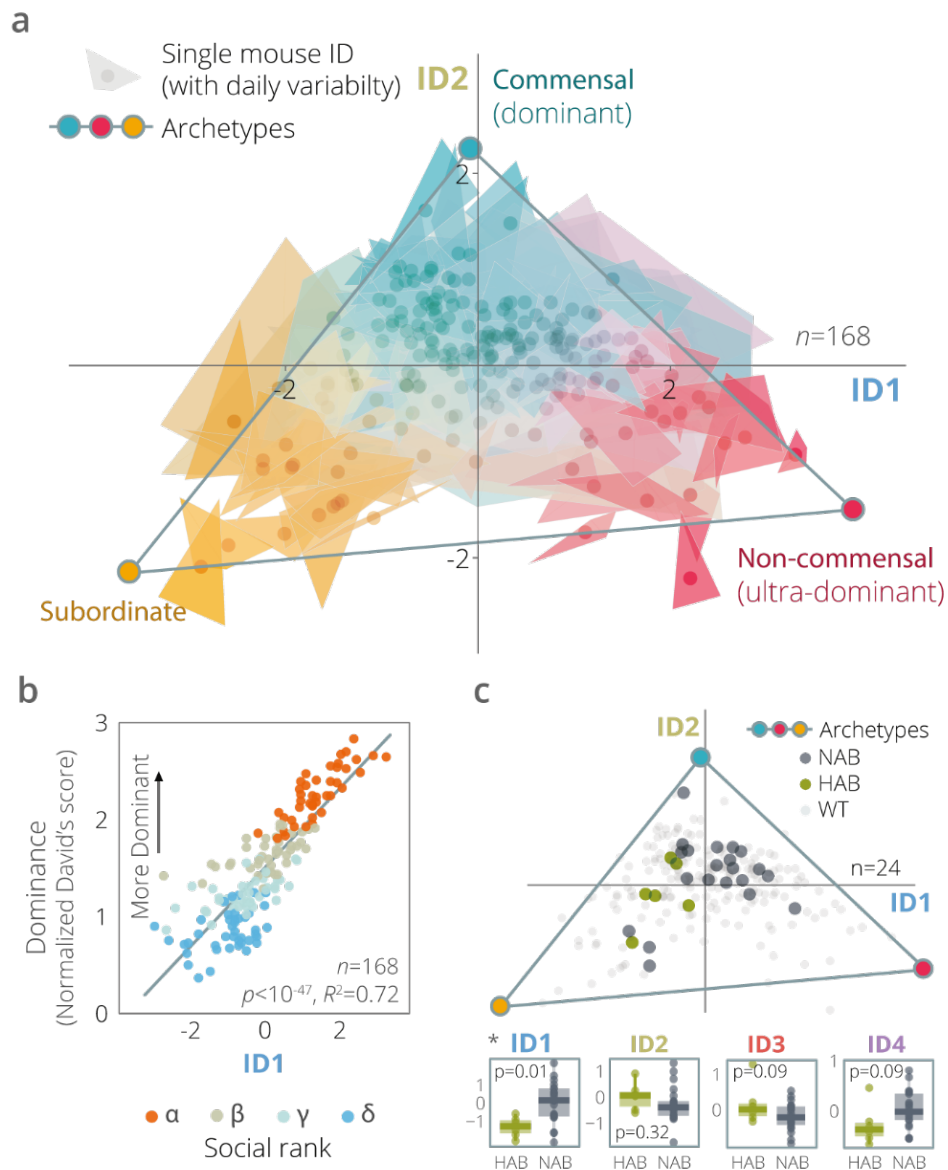
## 112 **IDs discriminate between genotypes**

113 Next, we tested the ability of IDs to capture and discriminate between individuals with known  
 114 genetically driven differences in behavioral tendencies. For this purpose, we used the high-  
 115 versus normal-anxiety (HAB/NAB) model, wherein mice are selectively bred over multiple  
 116 generations for different levels of anxiety-like behavior on the Elevated Plus Maze test<sup>5</sup>  
 117 (Supplementary Figure 8a). We monitored heterogeneous groups composed of one HAB and

118 three NAB individuals each in the Social Box and assigned ID scores to them. We were able to  
119 show that ID scores have considerable power in discriminating between the genotypes (Figure  
120 5c, Supplementary Figure 7b).

## 121 **Personality Space**

122 An important benefit that comes with having a known space of individual expression is the ability  
123 to search that space for points of biological interest, which may represent behavioral  
124 specializations. Using Pareto Task Inference, we found that ID1 and ID2 span a behavioral  
125 continuum on a triangle bounded by three personality archetypes (Figure 5a). Such a  
126 configuration can be interpreted as a tradeoff between 3 distinct evolutionary specializations, as  
127 previously shown for features of animal morphology<sup>6</sup> and *C. elegans* locomotion<sup>7</sup>. Analogous  
128 archetypes were found in the replication dataset.



**Figure 5.** Personality space. (a) The personality space captured by the first two IDs forms a triangle with three archetypes at its corners. These archetypes may correspond to three behavioral strategies that mice exhibit in nature: commensal, non-commensal (ultra-dominant), and subordinate. The ID scores of each individual are represented by a trapezoid with scores on each day marking the four corners (a triangle is depicted if the fourth point falls inside the shape). Thus, the size of each trapezoid reflects the stability of ID scores for each individual over time (smaller means more stable). (b) ID1 scores predict social dominance levels (David's Scores), calculated based on the number and directionality of aggressive interactions ( $p < 10^{-47}$ ). (c) Mice selectively bred for high and normal anxiety-like behavior levels (HAB/NAB) mice were assessed using the IDs. A significant genotype effect was detected by ID1 and ID4. The Pareto space reveals that HAB mice tend to be more subordinate (upper panel).

129 **Discussion**

130 Personality is a complex entity that reflects stable individual differences and, in so doing, maps  
131 the space of phenotypic variability. Here we show that IDs provide a bias-free surrogate measure  
132 of personality obtained directly from behavioral data. IDs show considerable stability over time,  
133 developmental stages, and across social contexts. They allow quantitative exploration of  
134 personality differences in organisms in which such analyses were previously inaccessible. By  
135 drawing on consistent inter-individual differences, IDs capture the essence of personality, thus  
136 offering access to a biologically meaningful and evolutionarily relevant meta-behavioral

## Methods

### Animals

137 All animal experiments were approved by the Animal Care and Use Committees of either the  
138 Government of Upper Bavaria (Munich, Germany) or the Weizmann Institute of Science (Rehovot,  
139 Israel).

140 Male CD-1 (ICR) mice aged 8 to 12 weeks during the assessment were used for all experiments  
141 with the exception of the high- vs. normal anxiety-like behavior animals (HAB/NABs, see below).  
142 The animals were housed in an SPF facility in temperature-controlled rooms under standard  
143 conditions with a 12h light/dark cycle (lights on at 8 am). After weaning, the animals were housed  
144 in groups of four non-siblings per cage. At around 7-8 weeks of age, the mice were transferred  
145 to the behavioral testing rooms and painted. All animals were housed in temperature-controlled  
146 environment with food and water available *ad libidum*.

### Painting

147 The fur of each mouse was painted to enable identification by automatic video tracking. Painting  
148 was carried out under mild isoflurane anesthesia using commercially available semi-permanent  
149 hair dyes of three colors: Pillarbox Red, Voodoo Blue, and Sunshine (Tish & Snooky's NYC Inc.,  
150 New York). A fourth, green hue, was achieved by mixing the latter two dyes. The dyes were  
151 applied using a paint brush. Excess color was removed from the animal's fur with tissues. The  
152 period under anesthesia was typically no longer than 10 min.

153 Mice were single-housed for several hours after painting and subsequently reunited with their  
154 cage mates. A minimum of 3 days of recovery/habituation was allowed following this procedure  
155 before the mice could be introduced into the social arenas.

### Social box setup

156 Mice were studied in a specialized arena designed for automated tracking of individual and group  
157 behavior. Each arena housed a group of four male mice. The arena consisted of an open 60 x 60

158 cm box and included the following objects: covered nest, open shelter, S-shaped wall, two water  
159 bottles, two feeders, and two elevated ramps. Food and water were available ad libitum. During  
160 the dark phase (12 hours) arenas were illuminated at 2 lux and during the light phase (12 hours)  
161 at 200 lux using LED lights. A color sensitive camera (Manta G-235C from Allied-Vision) was placed  
162 1 m above the arena and recorded the mice during the dark phase. Mouse trajectories were  
163 automatically tracked offline using specially written software in Matlab (Mathworks Inc.).

164 In order to validate the identity domains (IDs) and ensure repeatability, we also computed the ID  
165 scores for mice which were recorded in arenas of a different design<sup>3</sup>. These alternative arenas  
166 were 75 x 50 cm and included a covered nest, closed shelter (which is smaller than the nest, and  
167 has only one entry), two elevated ramps, two feeders, a single water bottle, an elevated block  
168 that is away from the walls, and a Z-wall.

#### Identification and classification of interactions between mice

169 We automatically identified and classified interactions between mice as events in which the  
170 distance between two mice ( $d$ ) was less than 10 cm. We then used the movement direction of  
171 one mouse relative to another mouse ( $\theta$ ) to identify the nature of the contact for either of the  
172 mice. If for mouse A, the projection of the direction of its movement relative to mouse B was  
173 small enough ( $|\tan(\theta) \cdot 2d| < \theta_1$ , for  $-\frac{\pi}{2} < \theta < \frac{\pi}{2}$ ) then it was considered as moving towards B; if  
174  $|\tan(\theta) \cdot 2d| < \theta_2$  for  $\frac{\pi}{2} < \theta < \frac{3}{2}\pi$  it was moving away from it; otherwise it was assumed idle with  
175 respect to the other mouse ( $\theta_1$  and  $\theta_2$  were found by optimization).

176 To classify aggressive and non-aggressive contacts, we first used a hidden Markov model<sup>8</sup> to  
177 identify post-contact behaviors in which mouse A was moving towards B, and B was moving away  
178 from A (A was following B). We then used 500 manually labeled events to learn statistical  
179 classifiers of aggressive and non-aggressive post-contact behavior. For each event, we estimated  
180 a range of parameters, including individual and relative speed, distance, etc. and optimized a  
181 quadratic discriminant classifier<sup>9</sup>, a k-nearest neighbor algorithm based on these parameters,  
182 and a decision-tree classifier, that used these parameters at each tree intersection<sup>10</sup>. We found  
183 that for a test set of 1000 events, none of these classifiers were accurate enough individually, but

184 that a combined approach in which we labeled an event as 'aggressive' if any of the classifiers  
185 labeled it as such – gave ~80% detection with 0.5% false alarms.

186

David's score for dominance

187 We used the Normalized David's score in order to assign each individual with a continuous  
188 measure of its social rank<sup>11</sup>. David's score assumes a linear hierarchy where each pair from the  
189 group includes a more and a less dominant individual. The score is based on the measure of the  
190 fraction of interactions in which mouse  $i$  chased mouse  $j$  relative to the total number of agonistic  
191 interactions, which we denote as  $P_{ij}$ . David's score of each individual is the sum

$$192 \quad DS_i = w^i + w_2^i - l^i - l_2^i$$

193 where  $w^i = \sum_{j \neq i} P_{ij}$  is the sum of the fraction of times that mouse  $i$  has "won" (i.e., was the  
194 chaser), and  $w_2^i = \sum_{j \neq i} w^j P_{ij}$  is a similar sum weighted by the  $w^j$  of the other mice, while  $l^i =$   
195  $\sum_{j \neq i} P_{ji}$  is the sum of the fractions of "losses" (escapes), and accordingly  $l_2^i = \sum_{j \neq i} w^j P_{ji}$  is its  
196 weighted sum. The score is then normalized to be between 0 and  $N-1$  (where  $N$  is the number of  
197 subjects, which equals 4 in our case) by using the following formula:

$$198 \quad NormDS = \frac{1}{N} \left( DS + \frac{N(N-1)}{2} \right).$$

Linear discriminant analysis

199 Linear discriminant analysis (LDA) is a method for finding a linear separator between two classes,  
200 or in its more general definition finding a subspace that best separates between multiple  
201 classes<sup>9,12,13</sup>. This subspace is obtained by finding a projection  $W$  which minimizes the Fisher-Rao  
202 discriminant defined as

$$203 \quad W = \underset{\hat{W}}{argmax} \operatorname{tr} \left( \frac{\hat{W}^T \Sigma_b \hat{W}}{\hat{W}^T \Sigma_w \hat{W}} \right).$$



204 This solution to this optimization problem can be found by reformulating it using a Lagrange  
205 multiplier  $\lambda$  as

$$206 \quad \mathcal{L}(W) = W^T \Sigma_b W - \lambda(W^T \Sigma_w W - 1)$$

207 and solving

$$208 \quad 0 = \frac{d}{dW} \mathcal{L}(W) = 2\Sigma_b W + 2\lambda \Sigma_w W.$$

209 The solution to this equation is obtained by finding the top eigenvectors of  $\Sigma_w^{-1} \Sigma_b$ .

Fisher-Rao discriminant

210 The Fisher-Rao discriminant is used to measure how distinct two or more classes of samples are.

211 The separation between classes is defined as the ratio of the variability between the classes  $\Sigma_b$   
212 to the variability within the classes  $\Sigma_w$

$$213 \quad D_{FR} = \text{tr} \left( \frac{\Sigma_b}{\Sigma_w} \right) = \text{tr} \left( \frac{\sum_{c=1}^C n_c (\mu_c - \mu)(\mu_c - \mu)^T}{\sum_{i=1}^n (x_i - \mu_{c_i})(x_i - \mu_{c_i})^T} \right),$$

214 where  $\mu$  is the global mean,  $\mu_{c_i}$  is the mean of the class associated with the  $i$ 'th sample  $x_i$ ,  $n_c$  is  
215 the number of samples in class  $c$ ,  $n = \sum_c n_c$  is the total number of data samples,  $C$  is the number  
216 of classes, and  $\text{tr}(\dots)$  is the trace function. The larger this ratio, the better the discriminability of  
217 the classes. Note that the sum of the within- and between-variability is proportional to the total  
218 covariance of the data ( $\Sigma$ )

$$219 \quad \Sigma = \frac{\Sigma_b + \Sigma_w}{n-1}.$$

Identity domains

220 Personality cannot be measured directly but it can be inferred from the behavior. We used the  
221 measured behavior of the mice for each of the four days they spent in the Social Box. The  
222 normalized measured behaviors of mouse  $m$  on day  $d$  are denoted by a vector  $x_{m,d}$  of dimension

223 60 (the number of behaviors; explanation of the normalization procedure follows). The ID  $I_m$   
224 defines a distribution on the behavior space in the following way

$$225 \quad x_{m,d} = A I_m + \varepsilon$$

226 where  $A$  is a matrix linking the IDs to the behaviors, and  $\varepsilon$  is a distribution term (or noise due to  
227 variability or external factors). In order to estimate the IDs, we need to reverse this equation and  
228 find a  $W$  that would give us

$$229 \quad I_m = W(x_{m,d} + \varepsilon)$$

230 Note that since  $A$  is not usually square  $W$  is not simply a reversal of  $A$ .

231 In order to find  $W$ , which in turn would give us the IDs, we used LDA. Here the variability-within  
232 is defined as the variability of the same individual mouse on different days, or

$$233 \quad \Sigma_w = \sum_{m=1}^M \sum_{d=1}^D \left( x_{m,d} - \sum_{d'=1}^D x_{m,d'} \right) \left( x_{m,d} - \sum_{d'=1}^D x_{m,d'} \right)^T$$

234 where  $M$  is the total number of mice ( $M=168$ ), and  $D$  is the total number of days ( $D=4$ ).  
235 Accordingly, the variability-within is the variability between mice or

$$236 \quad \Sigma_b = D \cdot \sum_{m=1}^M \left( \sum_{d=1}^D x_{m,d} - \mu \right) \left( \sum_{d=1}^D x_{m,d} - \mu \right)^T.$$

237 The link between the behavior and the IDs is obtained in the same way as in the classical LDA by  
238 solving

$$239 \quad W = \underset{\hat{W}}{\operatorname{argmax}} \operatorname{tr} \left( \frac{\hat{W}^T \Sigma_b \hat{W}}{\hat{W}^T \Sigma_w \hat{W}} \right).$$

240 Once we have  $W$ , we can also find  $A$  by solving it as a linear regression problem of the form

$$241 \quad x_{m,d} = A I_m + \varepsilon$$

242 In order to avoid batch effects and drifts of the data we used quantile normalization on each  
243 behavior for each batch on each day separately. We quantile-normalized the data to have a

244 normal distribution by computing the quantile of each sample and then computing the inverse  
245 of the normal cumulative distribution function (also known as the 'probit' function). If two or more  
246 samples were identical prior to the normalization they were all assigned the same value after  
247 normalization.

#### Pareto optimality

248 In order to survive and reproduce, animals are constantly confronted with tasks such as finding  
249 food or evading predators. Often there is a tradeoff between tasks, so that the success of an  
250 animal in one task has to come at the expense of its performance on another. Recent work has  
251 shown that the best phenotypes are the weighted average of archetypes, which are phenotypes  
252 that specialize in one task<sup>6,14</sup>. These phenotypes can either be morphological, as for the beak  
253 sizes of ground finches, or behavioral phenotypes.

254 The shape of the phenotype space is determined by the number of archetypes, or the number  
255 of tasks the animal faces: In case of two archetypes, optimal phenotypes would fall on the line  
256 connecting the two archetypes, while if there are three archetypes, the phenotypes would be  
257 contained inside a triangle, and so on.

258 One direct outcome of this theory is that looking at the whole phenotype space makes it possible  
259 to deduce the location of the archetypes and thereby the different biological challenges that an  
260 animal faces. The positions of the archetypes are found using a hyperspectral un-mixing  
261 algorithm. The data is first centered to have zero mean, and then projected using principal  
262 component analysis into a subspace with dimension  $n - 1$  (where  $n$  is the number of archetypes).  
263 Then an un-mixing algorithm is used in order to fit an  $n$  vertices polytope that best fits the data.  
264 Here we used minimal volume simplex analysis (MVSA), which is suitable for relatively small  
265 datasets since it does not allow for outliers. The analysis was performed in Matlab using the  
266 Pareto Task Inference (ParTI) package.

## Social box behavioral readouts

267 We collected a total of 60 different readouts for each mouse on each day. Due to the linearity of  
268 LDA, some of the behaviors we measured were computed with several different normalizations.  
269 The most common normalizations we used were: the total time in the arena (12 hours;  
270 abbreviated total), the time outside the nest (outside), and for interactions the total number of  
271 contacts (contacts).

### *Pairwise:*

- 272 • Time outside [1]: Fraction of time that the mouse spends outside of the nest.  
273 Normalizations: Total time (%).
- 274 • Frequency of visits outside [2]: The rate at which the mouse exits the nest. Normalizations:  
275 Total time (1/hour).
- 276 • Foraging correlation [3]: The correlation between the times that the mouse is outside the  
277 nest and the times that another mouse is outside the nest, averaged over all mice. For  
278 example, the foraging correlation between two mice would equal one if the mouse is  
279 always outside the nest when the other mouse is outside, and also enters the nest  
280 whenever the other mouse enters the nest. The correlation would be -1 whenever the  
281 mouse is outside, the other mouse is inside the nest. Normalizations: [3] none (au).
- 282 • Contact rate [4, 5]: Number of contacts the mouse had. A contact is defined as two mice  
283 being less than 10 cm apart while both are outside the nest. Normalizations: [4] Total time  
284 (1/hour), [5] Time outside (1/hour).
- 285 • Time in contact [6]: Fraction of time that a mouse is in contact with other mice while  
286 outside the nest. Normalizations: [6] Time outside (1/hour).
- 287 • Median\Mean contact duration [7, 8]: Median or mean duration of contacts. The contact  
288 duration does not include the times when the mouse approached, moved away from, or  
289 chased the other mouse. Normalizations: [7, 8] none (sec)
- 290 • Follow [12, 18, 24]: A follow is a contact that ended with one mouse going after another  
291 mouse until disengagement. Follows can be either aggressive (chases) or non-aggressive.

- 292 Normalizations: [12] Number of contacts (au), [18] Time outside (1/hour), [24] Total time  
293 (1/hour).
- 294 • Being-followed [13, 19, 25]: Number of times a mouse is followed at the end of a contact.  
295 It can be either in an aggressive (chases) or non-aggressive manner. Normalizations: [13]  
296 Number of contacts (au), [19] Time outside (1/hour), [25] Total time (1/hour).
  - 297 • Chase [10, 16, 22]: Chases are interactions that ended with the mouse pursuing another  
298 mouse in an aggressive manner. Aggressiveness was determined using a classifier that  
299 was trained on labeled samples (see methods). Normalizations: [10] Number of contacts  
300 (au), [16] Time outside (1/hour), [22] Total time (1/hour).
  - 301 • Escape [11, 17, 23]: Number of time that the mouse was aggressively chased by another  
302 mouse. Normalizations: [11] Number of contacts (au), [17] Time outside (1/hour), [23]  
303 Total time (1/hour).
  - 304 • Non-aggressive follow [14, 20, 26]: Number of times the mouse has followed another  
305 mouse at the end of a contact in a non-aggressive way. Normalizations: [14] Number of  
306 contacts (au), [20] Time outside (1/hour), [26] Total time (1/hour).
  - 307 • Non-aggressively being-followed [15, 21, 27]: Number of times the mouse was followed  
308 by another mouse at the end of a contact in a non-aggressive way. Normalizations: [15]  
309 Number of contacts (au), [21] Time outside (1/hour), [27] Total time (1/hour)
  - 310 • Approach [28, 29, 30, 31, 32]: An approach is a directed movement of the mouse towards  
311 another mouse that ends in contact. Not all interactions necessarily start with an  
312 approach, while others might start mutually with both mice approaching each other.  
313 Normalizations: [28] none (au), [29] Time outside (1/hour), [31] Number of contacts (au),  
314 [32] total (1/hour), [30] Time outside with one or more mice (1/hour).
  - 315 • Being-approached [33, 34, 35]: Number of times the mouse was approached by another  
316 mouse. Normalizations: [33] Number of contacts (au), [34] Time outside (1/hour), [35]  
317 none (au).
  - 318 • Approach-escape [36]: Fraction of contacts in which the mouse initiated the contact and  
319 ended up being chased. Normalizations: [36] Number of aggressive contacts (au).
  - 320 • Difference between approaches and chases [9]: The total number of chases is subtracted  
321 from the total number of approaches. Normalizations: [9] none (au).

*Individual:*

- 322       • ROI exploration [37, 38]: Quantifies the amount of exploration the mouse is doing.  
323       Measured as the entropy of the probability of being in each of the 10 regions-of-interest  
324       (ROIs). Mice that spend the same amount of time in all regions will get the highest score,  
325       while mice that spend all their time in a single ROI will be scored zero. When normalized  
326       to the time outside, the computation of the entropy differed also by ignoring the  
327       probability of being inside the nest. Normalizations: [37] none (bits), [38] Time outside  
328       (bits/hour).
- 329       • Grid exploration [59]: Quantifies the amount of exploration the mouse is doing.  
330       Analogously to 'ROI Exploration', grid exploration was determined using entropy,  
331       however, instead of looking at the ROIs, we divided the arena into a 6x6 grid (10 cm by 10  
332       cm; a total of 36 possible locations). Normalizations: [59] none (bits).
- 333       • Predictability [60]: Measures how predictable the paths that the mouse takes as the  
334       mutual information between its current and previous location in the arena. For that, the  
335       arena was divided into a 6x6 grid (10 cm by 10 cm; a total of 36 possible locations), and  
336       for each cell we computed the probabilities of it moving to any of the adjacent cells.  
337       Normalizations: [60] none (bits).
- 338       • Distance [58]: The total distance traveled by the mouse while outside the nest. To smooth  
339       the tracking, the mice locations were sampled once every second. Normalizations: [58]  
340       none (m).
- 341       • Median\Mean speed [54, 55]: Median or mean speed while outside the nest. To smooth  
342       the computation of the speed, the locations of mice were sampled once every second.  
343       Normalizations: [54, 55] none (m/sec).
- 344       • Tangential velocity [56]: The tangential component of the speed, or the part of speed  
345       perpendicular to the previous direction of movement. Normalizations: [56] none (m/sec).
- 346       • Angular velocity [57]: The rate of change in the direction of the mouse. Normalizations:  
347       [57] none (rad/sec).
- 348       • Food or water [39, 40]: Time spent next to the feeders or water bottles. Normalizations:  
349       [39] Total time (au), [40] Time outside (au)

- 350 • Food [41]: Time spent next to the feeders. Normalizations: [41] Time outside (au).
- 351 • Water [42]: Time spent next to the water bottles. Normalizations: [42] Time outside (au).
- 352 • Feeder preference [43]: Time spent in the feeder adjacent to the nest (feeder 1) relative  
353 to the further-away feeder (feeder 2). Normalizations: [43] none (au).
- 354 • Water preference [44]: Time spent near the water bottle adjacent to the nest (water 1)  
355 relative to the further-away water bottle (water 2). Normalizations: [44] none (au).
- 356 • Elevated area [45, 46]: Time spent on an elevated object in the arena: ramps or block (in  
357 the other arena setting). Normalizations: [45] Total time (au), [46] Time outside (au).
- 358 • Open area [47]: Time spent in the open area (outside of the nest and any of the ROIs).  
359 Normalizations: [47] Time outside (au).
- 360 • Shelter [48]: Time spent in the shelter, which is a box closed only on its sides.  
361 Normalizations: [48] Time outside (au).
- 362 • Ramps [49]: Time spent on the elevated ramps. Normalizations: [49] outside (au).
- 363 • S-wall [50]: Time spent in the S-wall. Normalizations: [50] Time outside (au).
- 364 • Distance from walls [51]: Average distance from the walls while in the open area.  
365 Normalizations: [51] none (cm).
- 366 • Distance from nest [52]: Average distance from the nest (while outside of the nest).  
367 Normalizations: [52] none (cm).
- 368 • Alone outside [53]: Fraction of time the mouse is outside while all other mice are in the  
369 nest. Normalizations: [53] Total time (au).

### Standard behavioral assays

370 All behavioral tests were performed several days after the social arena assessment in the same  
371 test room in two batches of 8 groups each using two different test sequences. During this time,  
372 the mice were housed in their original groups.

373 Timeline 1 consisted of the open field (OF)/novel object recognition (NOR) test, social preference  
374 test (SPT), and dark-light transfer (DaLi) test. Timeline 2 consisted of the OF/NOR, followed by the  
375 elevated plus maze (EPM), DaLi, SPT, and forced swim (FST) tests. In both cases, each test was  
376 followed by a minimum of 48 hours of rest.

### *Open field and novel object recognition tests*

377 The OF and NOR tests were performed in 60 x 60 cm boxes under minimal illumination (2-3 lux)  
378 in three sessions. Each animal was introduced to the arena for 5 min, then briefly removed and  
379 reintroduced for 5 more minutes to the same arena, now with two identical objects placed at  
380 predetermined locations. Finally, each animal was reintroduced to the arena after a 4 h delay for  
381 5 minutes with one of the two identical objects replaced by a novel one<sup>15</sup>. Object preference was  
382 calculated as the novel/familiar object ratio, while the discrimination index was calculated as the  
383 ratio of preference to phase 2 total exploration time.

### *Dark-light transfer and elevated plus-maze tests*

384 Anxiety-like behaviors were assessed using the DaLi or EPM tests performed in standard  
385 behavioral apparatuses. The illumination of the light sections of each apparatus was set at 200  
386 lux and the duration of both tests was set to 5 min.

### *Forced swim test*

387 Behavioral despair was measured using the FST. Each animal was placed in a 2 L transparent  
388 beaker filled halfway with room-temperature water for 6 min. Floating, swimming, and struggling  
389 times were manually scored by experienced observers.

### *Social preference test*

390 The SPT was performed under low illumination (2 lux) over three sessions in a three-chamber  
391 apparatus. This consisted of a middle chamber connected to two chambers on each side by a  
392 door. An empty metal grid cone was placed in the center of each of the two side-chambers.  
393 During the first session, the doors to the side chambers were closed and each test mouse was  
394 introduced into the middle chamber and allowed to habituate to it for 5 min. The doors were  
395 subsequently opened and a stimulus CD-1 mouse was placed under one of the metal grid cones,  
396 the other remaining empty, for 10 minutes. Sociability was calculated based on this session as  
397 the ratio of time spent in the chamber with the stimulus mouse to time in the chamber with the  
398 empty cone, weighted by total time spent in both of these chambers. Finally, in a following 10



399 min session, a different stimulus mouse was placed under the other cone. Preference for social  
400 novelty was assessed using the ratio of time with novel versus familiar mouse weighted by total  
401 time in either chamber.

#### *Y-maze alternation task*

402 Working memory was assessed using the Y-maze alternation task. Each mouse was introduced  
403 for 5 min into a Y-shaped three-arm apparatus with distinguishing visual cues on the walls at the  
404 end of each arm. The proportion of spontaneous non-repeated subsequent entries into each of  
405 the three arms (alternations) from the total number of three-arm entries (including repeat  
406 entries) was used as the final readout.

#### *Resident-intruder test*

407 Aggression toward an unfamiliar intruder mouse was assessed using a resident-intruder  
408 paradigm. For this test, each mouse was single-housed in a fresh type 2 cage. At each time point,  
409 48, 72, and 96 h after single-housing, an intruder C57/BL6 mouse was introduced into the cage.  
410 Latency to first aggressive interaction was assessed by an observer. Each trial was interrupted  
411 after the first overtly aggressive confrontation or after 15 min.

#### *Holeboard exploration test*

412 Exploratory behavior was measured in the holeboard exploration test. Each mouse was  
413 introduced for 5 min into a 40 x 40 cm arena surrounded by transparent Plexiglas walls with 4 x  
414 4 equally spaced holes on the floor. Number of head dips into any hole as well as number of  
415 rearings during the test interval were assessed by an observer.

#### *RNA-sequencing*

416 Brains were dissected from animals sacrificed with an overdose of isoflurane and flash-frozen.  
417 Tissue samples were cryopunched using a 1 mm diameter punching tool at Bregma 1.98 mm  
418 (medial prefrontal cortex (PFC), insular cortex (INS), 600 um depth) or an 0.8 mm diameter punch  
419 at Bregma -0.7 mm (basolateral amygdala (BLA), 1000 um depth) according to Paxinos and

420 Franklin, 1998. Total RNA was isolated using the miRNeasy micro kit (QIAGEN) after  
421 homogenization by a Bullet Blender (Next Advance). Residual genomic DNA was removed using  
422 the Turbo DNA-free kit (Ambion®, Invitrogen, CA, USA). RNA integrity and absence of DNA was  
423 confirmed by an Agilent RNA ScreenTape (4200 TapeStation, Agilent, eRIN all >7.8) and Qubit DNA  
424 High sensitivity kit, respectively. Sequencing libraries were prepared using the Illumina TruSeq  
425 Stranded Total RNA Library Preparation HT Kit using mammalian RiboZero Gold following the  
426 standard protocol starting from 300 ng (PFC), 500 ng (INS), and 375 ng (BLA) of total RNA using  
427 12 cycles of PCR amplification. Libraries were quality-checked using Bioanalyzer DNA High  
428 Sensitivity chips (Agilent Technologies, St. Louis, MO) and quantified using the KAPA Library  
429 Quantification Kit (KAPA Biosystems, Boston, MA). Sequencing was performed on 6 lanes of an  
430 Illumina HiSeq4000 PE 2x100 (Illumina, San Diego, CA) multiplexing all samples.

431 Sequencing was performed on a HiSeq4000 generating 100 base pair paired-end reads. Read  
432 quality was checked using FastQC<sup>16</sup> and subsequently adapters were trimmed using cutadapt<sup>17</sup>.  
433 For quantification of transcript expression levels, Kallisto<sup>18</sup> was executed using Gencode M11  
434 annotation and collapsed to gene level.

435 Count data was pre-filtered for low counts at a threshold of  $\geq 20$  counts per sample in a minimum  
436 of 31 out of 32 samples per region. In addition, the top three most highly expressed genes were  
437 excluded, resulting in a total list of 13,073 genes. Differential gene expression analyses were  
438 performed in DESeq2<sup>19</sup>. Heteroscedasticity in the data was reduced using the DESeq2 regularized  
439 logarithm transformation. The plate row of each sample was identified as a potential batch effect  
440 and corrected for using the limma package<sup>20</sup>.

441 The normalized and log-transformed count data was then used as the outcome of a linear model  
442 with either the real or the shuffled ID scores (day 1 in the social box) as predictors ( $rlog(count) =$   
443  $ID1 + ID2 + ID3 + ID4 + \epsilon$ ). Total variance explained by the model, as well as the fraction of variance  
444 explained by each individual predictor were estimated using the variancePartition package<sup>21</sup>. Two  
445 hundred models with shuffled ID scores were run per region to generate a distribution of mean  
446 variance explained across all genes and the model with the real ID scores was tested against this  
447 distribution using a one-sample t-test.

#### Code availability

448 All the code used in the LDA implementation in MATLAB will be made available upon request.  
449 Likewise, the self-similarity tests implemented in MATLAB, as well as the R code used in the RNA-  
450 seq data analysis will be made available upon request.

#### Data availability

451 The datasets generated during and/or analyzed during the current study are available from the  
452 corresponding author on reasonable request.

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## Supplementary Information

491 Supplementary Figures 1-9

492 Movie 1: A representative segment from a video recording of the social arenas with a group of  
493 four colored mice. Overlaid on top of the video are illustrations of tracked mouse movements  
494 and the layout and components of the social arena.

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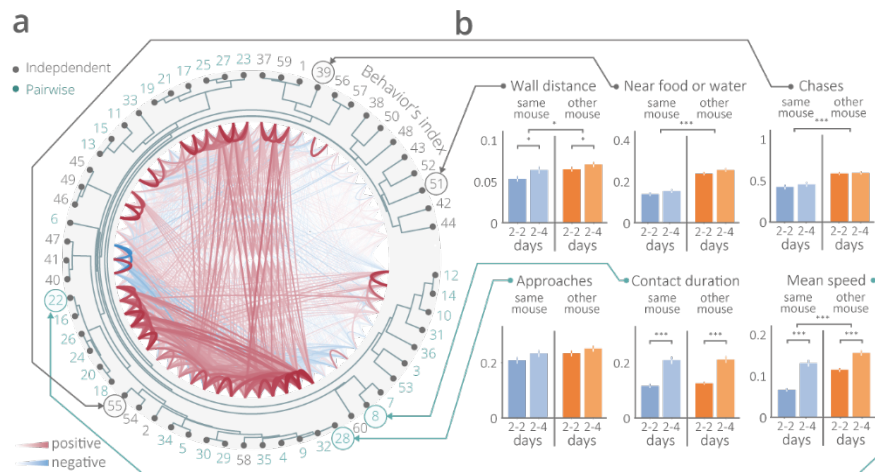
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#### Author contributions

513 O.F and S.K. designed the experiments, analyzed the results, and wrote the manuscript. M.N.,  
514 C.F., and P.K. assisted in experiments. M.E. performed the sample collection and RNA-sequencing  
515 library preparation. S.R. performed the preprocessing of the RNA-sequencing data and  
516 contributed to the final analyses. U.A., S.A., and Y.S. contributed to the manuscript. A.C.  
517 supervised and supported the project.

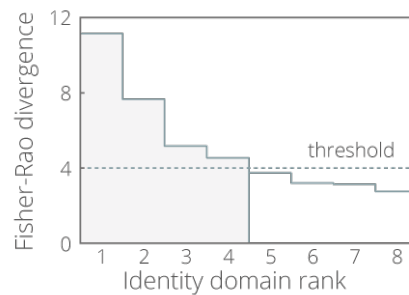
518 The authors declare no competing financial interests.

## Supplementary Figure 1



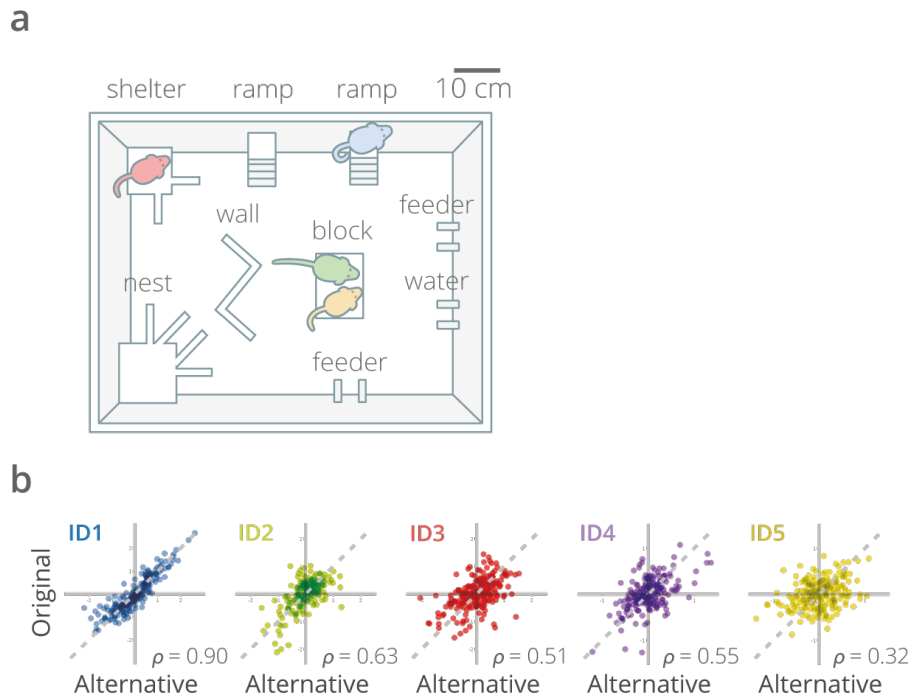
**Supplementary Figure 1 | Individual differences and consistencies.** (a) Behavioral readout structure. Hierarchical clustering and cross-correlations of the 60 behavioral readouts. Behavioral readouts tend to cluster based on whether they are independent (related to 1 mouse) or pairwise (derived from the locations of 2 mice). (b) Some behavioral parameters were consistent within individuals over time (e.g., approaches, chases), while some parameters could discriminate between individuals (e.g., mean speed, wall distance; \*\*\* $p<0.001$ , \* $p<0.05$ ).

## Supplementary Figure 2



**Supplementary Figure 2 | Between-within variability ratio.** Identity domain (ID) components ranked by their Fisher-Rao coefficient. Four components had a Fisher-Rao-score below 4, indicating a greater contribution of between over within-individual variability.

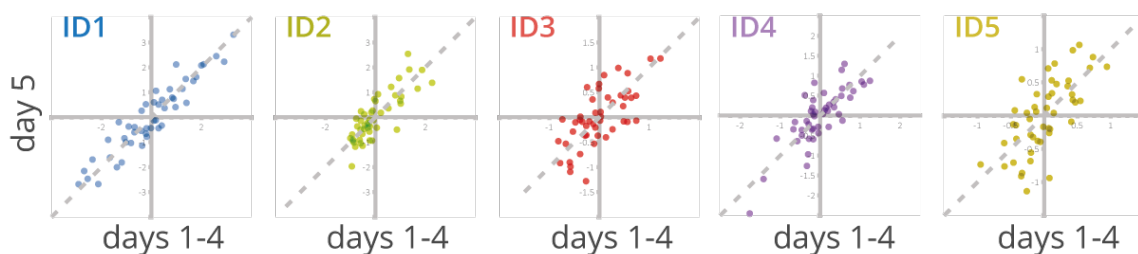
### Supplementary Figure 3



**Supplementary Figure 3 | Validation of the identity domains (IDs) in a second dataset from an alternative setup.** (a) Alternative social arena (50 x 70 cm) with a different locations and types of objects compared to arena shown in Figure 1 (b). (b) IDs 1-4 show intermediate to strong correlations between the original and replication datasets.

520

### Supplementary Figure 4

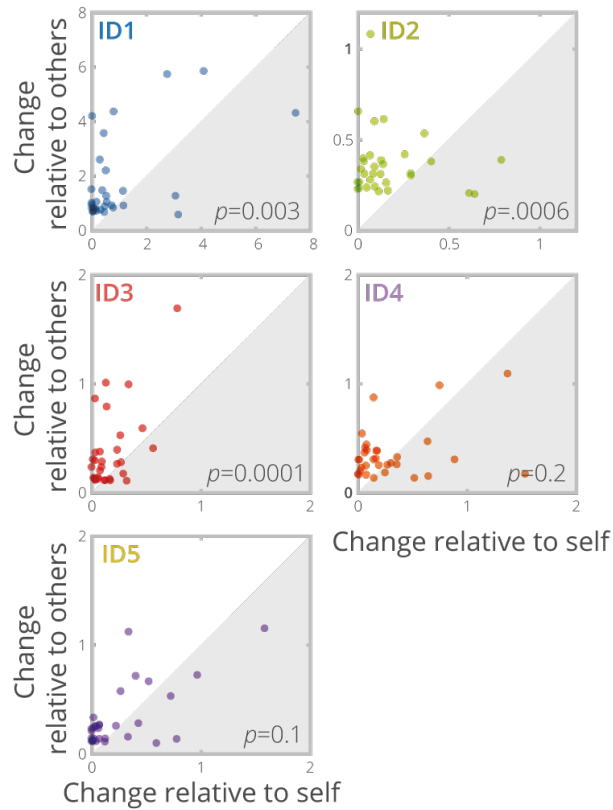


**Supplementary Figure 4 | Identity domain (ID) stability over a short timescale.** IDs were stable over experimental time, such that average ID scores for experimental days 1 through 4 could predict the corresponding scores for each animal on day 5.



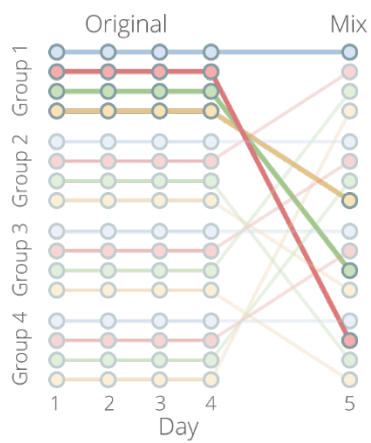
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Supplementary Figure 5



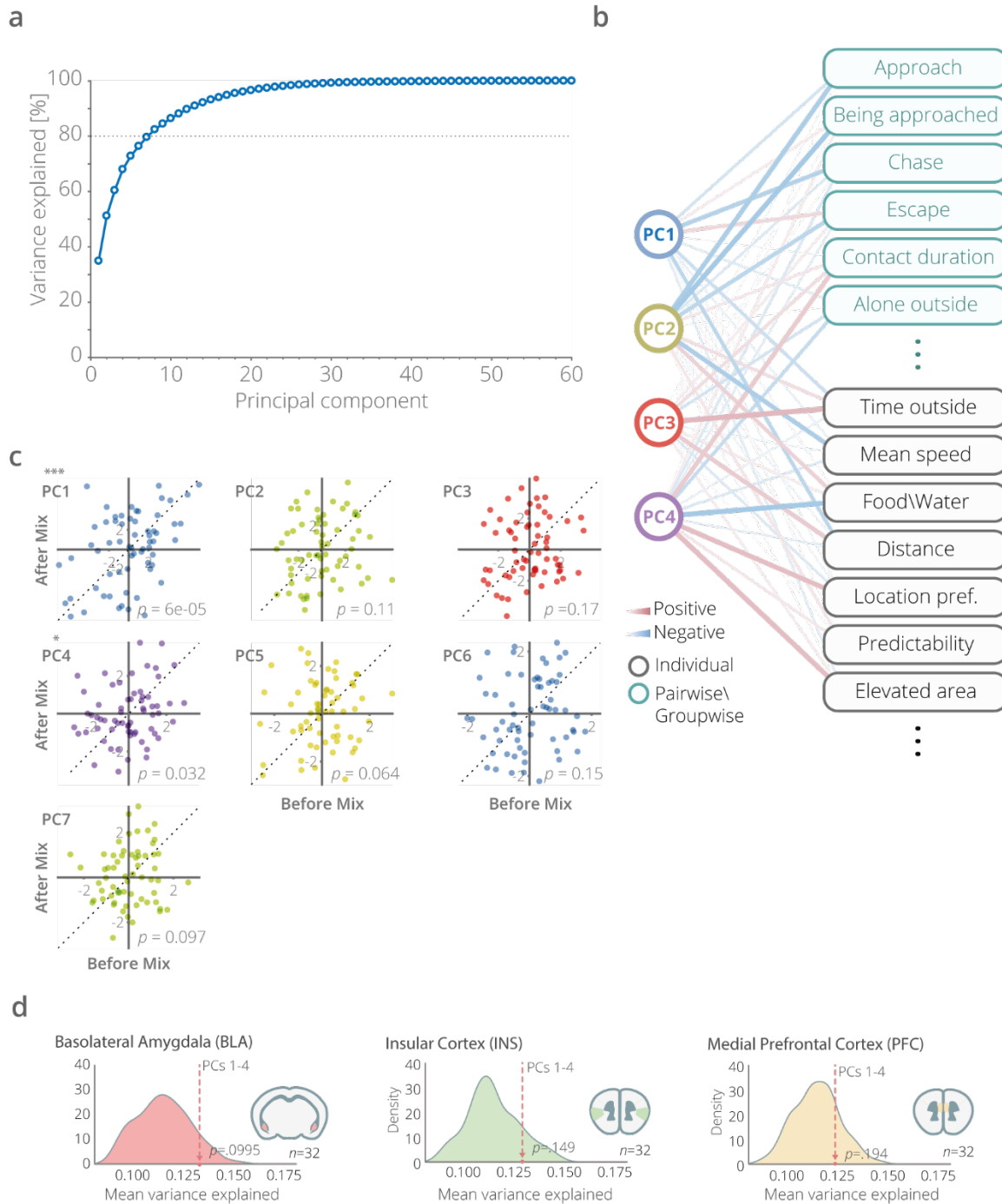
**Supplementary Figure 5 | Change over time with respect to self or others.** ID stability during aging was tested by comparing the ID scores of individuals measured once juveniles (4-5 weeks old) and once more during adulthood (15-16 weeks old). Depicted here are change in ID scores relative to one's own initial score versus relative to the scores of all other individuals. Points in the shaded region represent greater individual changes, whereas points in the unshaded region represent changes that were larger relative to other individuals than to oneself.

## Supplementary Figure 6



**Supplementary Figure 6 | Group shuffle diagram.** Mice were observed in the social boxes over 4 days and re-grouped on day 5 such that no mouse was familiar with any of its new conspecifics ( $n = 64$ , 16 groups).

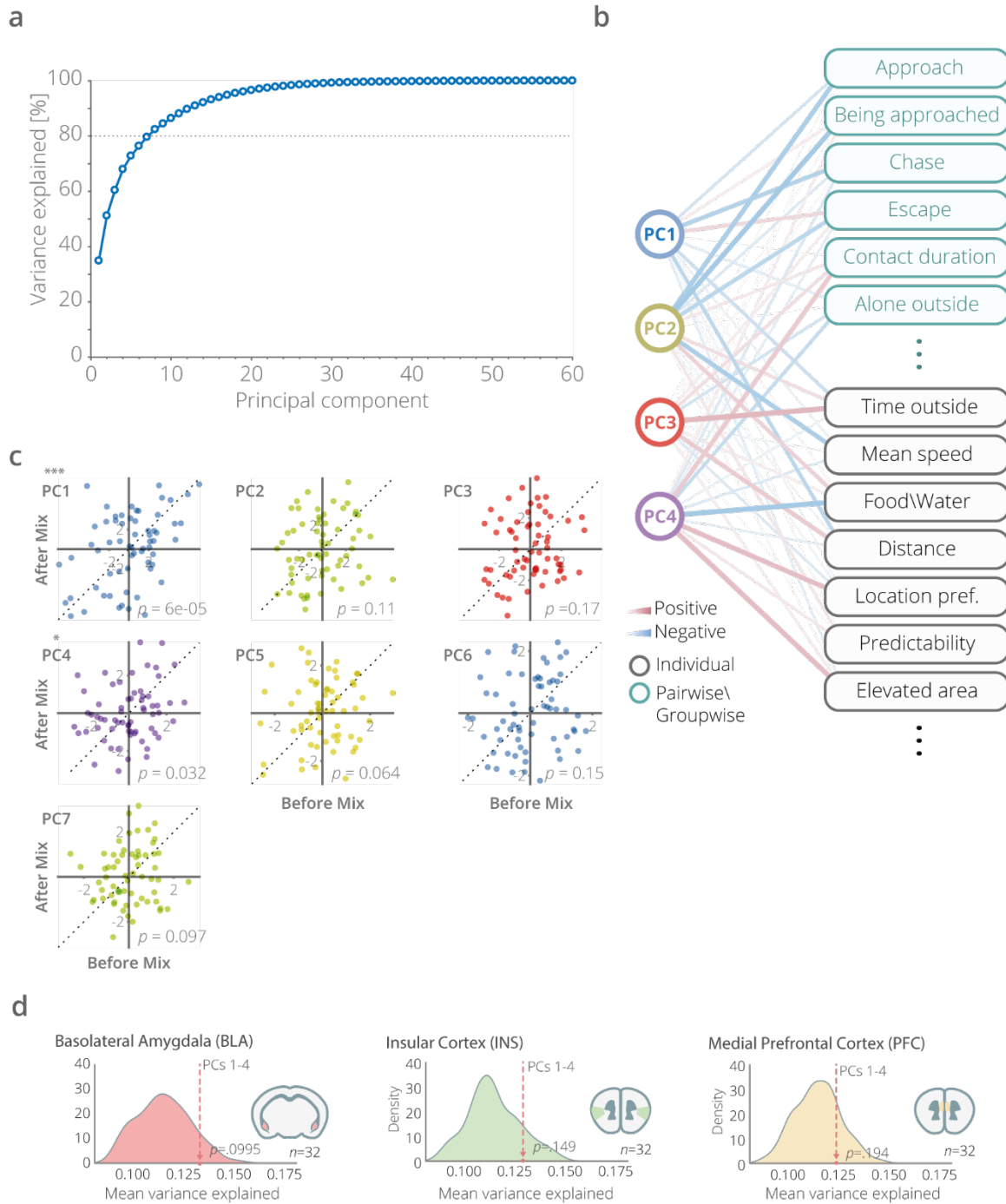
## Supplementary Figure 7



**Supplementary Figure 7 | Principal components analysis (PCA) on the initial set of behaviors.** In order to compare how LDA performs relative to better-known and more commonly used dimension reduction method, PCA was performed on the same initial dataset as used to generate the IDs. (a) The percent variance of the behavioral data explained by each principal component (PC). (b) Correlations between scores on each PC and an abbreviated list of behavioral readouts. (c) The stability of PC scores was tested as with the IDs before and after mixing the mouse groups such that all individuals were unfamiliar to one another. Only the first principal component remained stable after the mix. (d) Scores on the first four PCs were used as predictors of transcriptomic variance in RNA-sequencing data from three different brain regions. This analysis directly mimicked the equivalent analysis performed using the four IDs (PC scores from day 1, 200 shuffled PC score sets). The top four PCs did not carry more overall transcriptomic information than would be expected by chance.

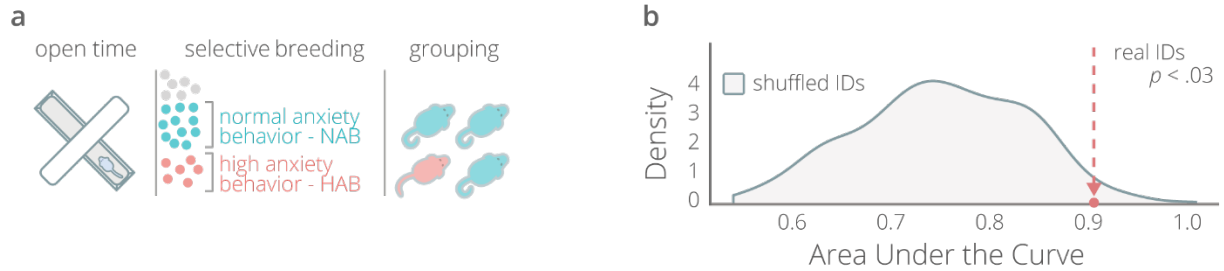
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## Supplementary Figure 8



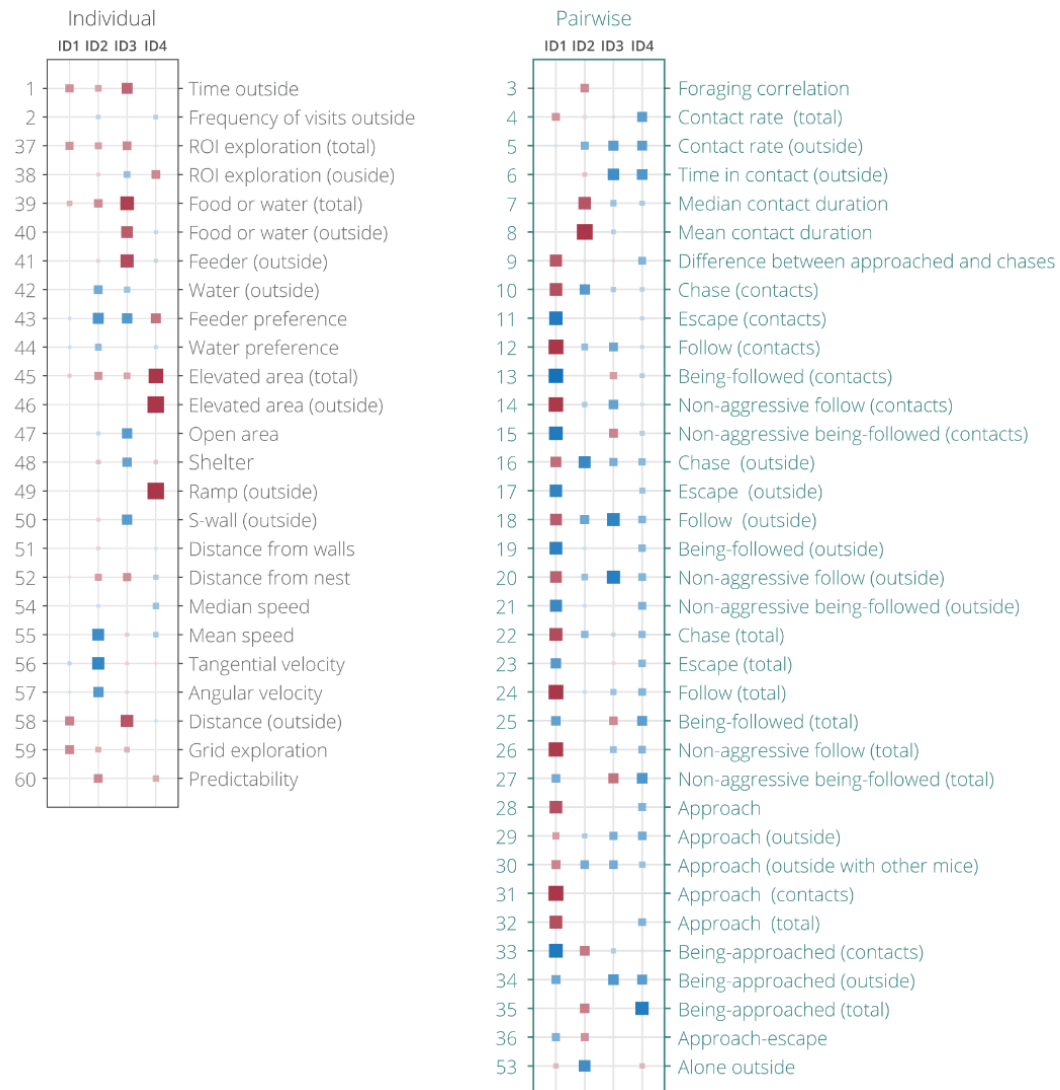
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**Supplementary Figure 8 | High-anxiety (HAB) versus normal-anxiety (NAB) mouse model.** (a) Selective breeding for high versus normal anxiety-like behavior levels (HAB/NAB) was performed for over > 40 generations starting with outbred CD-1 mice<sup>5</sup>. Selection was based on results of the Elevated Plus Maze test (% time in the open arm). After the animals of each respective genotype were weaned, they were mixed into groups of three NABs and one HAB each. (b) The power of the identity domain (ID) scores to detect genotype was tested directly using the area under the receiver operating characteristic curve of a model predicting genotype based on IDs 1-4. The area under the curve of this model was compared against a distribution created based on 200 trials with shuffled ID scores.

## Supplementary Figure 9



**Supplementary Figure 9 | Correlations between identity domains (IDs) and their contributing behavioral readouts.** The readouts are separated into individual (based on the movements of a single mouse) and pairwise (based on the movements of a mouse and one more of its group members).