

¹ **Whole-brain comparison of rodent and human brains
2 using spatial transcriptomics**

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¹⁷ **Abstract**

¹⁸ The ever-increasing use of mouse models in preclinical neuroscience research calls for an improvement in the
¹⁹ methods used to translate findings between mouse and human brains. Previously we showed that the brains
²⁰ of primates can be compared in a direct quantitative manner using a common reference space built from
²¹ white matter tractography data (Rogier B. Mars et al., 2018b). Here we extend the common space approach
²² to evaluate the similarity of mouse and human brain regions using openly accessible brain-wide transcrip-
²³ tomic data sets. We show that mouse-human homologous genes capture broad patterns of neuroanatomical
²⁴ organization, but that the resolution of cross-species correspondences can be improved using a novel su-
²⁵ pervised machine learning approach. Using this method, we demonstrate that sensorimotor subdivisions of
²⁶ the neocortex exhibit greater similarity between species, compared with supramodal subdivisions, and that
²⁷ mouse isocortical regions separate into sensorimotor and supramodal clusters based on their similarity to
²⁸ human cortical regions. We also find that mouse and human striatal regions are strongly conserved, with
²⁹ the mouse caudoputamen exhibiting an equal degree of similarity to both the human caudate and putamen.

30 Introduction

31 Animal models play an indispensable role in neuroscience research, not only for understanding disease and
32 developing treatments, but also for obtaining data that cannot be obtained in the human. While numerous
33 species have been used to model the human brain, the mouse has emerged as the most prominent of these,
34 due to its rapid life cycle, straightforward husbandry, and amenability to genetic engineering (Dietrich et
35 al., 2014; Ellenbroek and Youn, 2016; Hedrich et al., 2004; Houdebine, 2004). Mouse models have proven
36 to be extremely useful for understanding diverse features of the brain, from its molecular neurobiological
37 properties to its large-scale network properties (Hodge et al., 2019; Oh et al., 2014; Yao et al., 2021).
38 However, translating findings from the mouse to the human has not been straightforward. This is especially
39 evident in the context of neuropsychopharmacology, where promising neuropsychiatric drugs have one of the
40 highest failures rates in Phase III clinical trials (Hay et al., 2014).

41 Successful translation requires an understanding of how effects on the brain of the model species are likely to
42 manifest in the brain of the actual species of interest. This is not trivial in the case of the mouse and human,
43 as the two species diverged from a common ancestor about 80 million years ago (Kaas, 2012). Although
44 common themes are apparent in the brains of all mammalian species studied to date (Krubitzer, 2007), there
45 remain substantial differences between the mouse and human brain. Beyond the obvious differences in size,
46 large parts of the human cortex potentially have no corresponding homologues in the mouse (Preuss, 1995).
47 Direct comparisons across the brains of different species are further complicated by the fact that researchers
48 from different traditions use inconsistent nomenclature to refer to similar neuroanatomical areas (Heukelum
49 et al., 2020; Laubach et al., 2018).

50 Over the course of the last decade, we have developed novel approaches to explicitly evaluate similarities
51 and differences between the brains of related species. These approaches describe brains using common data
52 spaces that are directly comparable between species, making it possible to evaluate the similarity of different
53 regions in a quantitative fashion (Mars et al., 2021). This way, potential homologues can be formally tested
54 and regions of the brain that do not allow for straightforward translation can be identified (Rogier B. Mars
55 et al., 2018b). Establishing such a formal translation between the mouse and the human brain would allow
56 scientists involved in translational research to explicitly test hypotheses about conservation of brain regions,
57 identify regions that are well suited to translational paradigms, and directly transform quantitative maps
58 from the brain of one species to the other.

59 One approach towards building these common spaces has been to exploit connectivity. It has previously
60 been demonstrated that brain regions can be identified via their unique set of connections to other regions

61 in the brain. This *connectivity fingerprint* can therefore be seen as a diagnostic of an area (Rogier B. Mars
62 et al., 2018a; Passingham et al., 2002). The common connectivity space approach relies on defining agreed
63 upon neuroanatomical homologues a priori and then expressing the connectivity fingerprint of regions under
64 investigation with those established homologues in the two brains (Mars et al., 2016b). The connections
65 of any given region to the established homologues thus form a common space, which links the two brains.
66 In a series of early studies, we compared the connectivity of the macaque and human brain, identifying
67 homologies as well as specializations across association cortex (Mars et al., 2013; Neubert et al., 2014; Sallet
68 et al., 2013). The same approach has recently been applied to mouse-human comparisons for the first time,
69 demonstrating conserved organization between the mouse and human striatum, but some specialization in
70 the human caudate related to connectivity with the prefrontal cortex (Balsters et al., 2020). A similar study
71 recently compared connectivity of the medial frontal cortex across rats, marmosets, and humans (Schaeffer et
72 al., 2020). However, the lack of established neuroanatomical homologues in mice, particularly in the cortex,
73 limits the use of connectivity to compare these species.

74 A more promising approach to mouse-human comparisons could be to exploit the spatial patterns of gene
75 expression. Advances in transcriptomic mapping can be used to characterise the differential expression of
76 many thousands of genes across the brain and compare the pattern between regions (Ortiz et al., 2020).
77 Moreover, the availability of whole-brain spatial transcriptomic data sets for multiple species provides an
78 opportunity to run novel analyses at low cost (Hawrylycz et al., 2012; Lein et al., 2007). Such maps for the
79 human cortex show topographic patterns that mimic those observed in other modalities, such as a gradient
80 between primary and heteromodal areas of the neocortex (Burt et al., 2018). Importantly, these patterns
81 appear to be conserved across mammalian species (Fulcher et al., 2019), which opens up the possibility
82 of using the expression of homologous genes as a common space across species. In fact, a recent study
83 demonstrated how the expression of homologous genes can be used to directly register mouse and vole brains
84 into a common reference frame, which allows for direct point-xby-point comparisons of brain maps (Englund
85 et al., 2021). However, this specific approach is only feasible because of the large degree of morphological
86 similarity between mouse and vole brains. In the case of mouse-human comparisons, we almost certainly
87 cannot directly register mouse and human brains into a common coordinate frame using methods for image
88 registration. Hence we need to be more creative in our approach.

89 Here we examine the patterns of similarity between the mouse and human brain using a common space
90 constructed from spatial gene expression data sets. We begin with an initial set of 2835 homologous genes.
91 Subsequently, we present and evaluate a novel method for improving the resolution of mouse-human neu-
92 roanatomical correspondences using a supervised machine learning approach. Using the novel representation

93 of the gene expression common space, i.e. a latent gene expression space, we analyse the similarity of mouse
94 and human isocortical subdivisions and demonstrate that sensorimotor regions exhibit a higher degree of sim-
95 ilarity than supramodal regions. Finally, we examine the patterns of transcriptomic similarity at a voxel-wise
96 level in the mouse and human striatum.

97 Results

98 Homologous genes capture broad similarities in the mouse and human brains

99 We first examined the pattern of similarities that emerged when comparing mouse and human brain regions
100 on the basis of their gene expression profiles. We constructed a gene expression common space using widely
101 available data sets from the Allen Institute for Brain Science: the Allen Mouse Brain Atlas (AMBA) and
102 the Allen Human Brain Atlas (AHBA) (Hawrylycz et al., 2012; Lein et al., 2007). These data sets provide
103 whole-brain coverage of expression intensity for thousands of genes in the mouse and human genomes. For
104 our purposes we filtered these gene sets to retain only mouse-human homologous genes using a list of ortho-
105 logues obtained from the NCBI HomoloGene system (NCBI 2018). Using a gene enrichment analysis, we
106 found that this reduced gene set was significantly associated with a number of biological processes related to
107 the nervous system, with Gene Ontology labels such as “nervous system development”, “neurogenesis”, and
108 “regulation of nervous system development”. Additional modules returned with high significance were “reg-
109 ulation of multicellular organismal process”, “regulation of biological quality”, and “multicellular organism
110 development”. The full set of significant modules can be found in Supplementary File 1.

111 Prior to analysis, the mouse and human homologous gene expression data sets were pre-processed using a
112 pipeline that included quality control checks, normalization procedures, and aggregation of the expression
113 values under a set of atlas labels. The result was a gene-by-region matrix in either species, describing the
114 normalized expression of 2835 homologous genes across 67 mouse regions and 88 human regions (see Materials
115 and methods). We quantified the degree of similarity between all pairs of mouse and human regions using
116 the Pearson correlation coefficient, resulting in a mouse-human similarity matrix (Figure 1A).

117 We find that the similarity matrix exhibits broad patterns of positive correlation between the mouse and
118 human brains. These clusters of similarity correspond to coarse neuroanatomical regions that are generally
119 well-defined in both species. For instance, we observe that, overall, the mouse isocortex is similar to the
120 human cerebral cortex, with the exception of the hippocampal formation, which forms a unique cluster.
121 Similarly the mouse and human cerebellar hemispheres cluster together, while the cerebellar nuclei show

122 relatively high correlation to each other ($r = 0.404$) as well as to brain stem structures like the pons ($r = 0.359$
123 and $r = 0.371$ for the mouse and human nuclei respectively) and myelencephalon ($r = 0.318$ and $r = 0.374$).
124 The associations between broad regions such as these are self-evident in the correlation matrix.

125 Our ability to resolve regional matches on a finer scale is limited when using all homologous genes in this way.
126 This is especially true for regions within the cerebral and cerebellar cortices, which exhibit a high degree
127 of internal homogeneity. This is apparent in the similarity profiles, defined here as the set of correlation
128 values between a given seed region and all target regions in the other species. For example, the human
129 precentral gyrus and cuneus are most strongly correlated to many regions of the mouse isocortex. While
130 the brain maps feature a rostral-caudal gradient (Figure 1B), the profiles of the two seeds are highly similar
131 despite the regions having very different functions (Figure 1C). Indeed, the correlation between the similarity
132 profiles of the precentral gyrus and cuneus is $r = 0.980$. The similarity profile of human cerebellar crus 1
133 highlights another example of this homogeneity. The profile of crus 1 is similar to that of all regions of the
134 mouse cerebellum, with an average correlation of $r = 0.269$ and a standard deviation of $\sigma = 0.041$. Across
135 all regions, the variance of the correlations across cortical regions is $\sigma^2 = 0.0052$ while that across cerebellar
136 hemispheric regions is $\sigma^2 = 0.0017$, compared with a total variation of $\sigma^2 = 0.0416$ across all entries in the
137 matrix.

138 So, although there is some distinguishing power in the profiles of regions at a finer scale, this is much smaller
139 than between coarse anatomical regions. This is also true for parts of the broad anatomical systems that are
140 part of the same functional system. This suggests that the regional expression patterns of mouse-human
141 homologous genes can be used to identify general similarities between the brains of the two species even
142 using a simple correlation measure, but the ability to identify finer scale matches might require a more
143 subtle approach.

144 **A latent gene expression space improves the resolution of mouse-human associations**
145

146 In the previous analyses, we showed that the expression profiles of homologous genes capture broad simi-
147 larities across the mouse and the human for the major subdivisions of the brain. Some information at a
148 finer resolution (e.g. within the isocortex) was also evident, but much less distinctive. Our next goal was
149 to investigate whether it is possible to leverage the gene expression data sets to relate mouse and human
150 brains to one another at a finer regional level. In order to do so, we sought to maximise the informational
151 value in the set of 2835 homologous genes by creating a new latent common space that exploits the regional

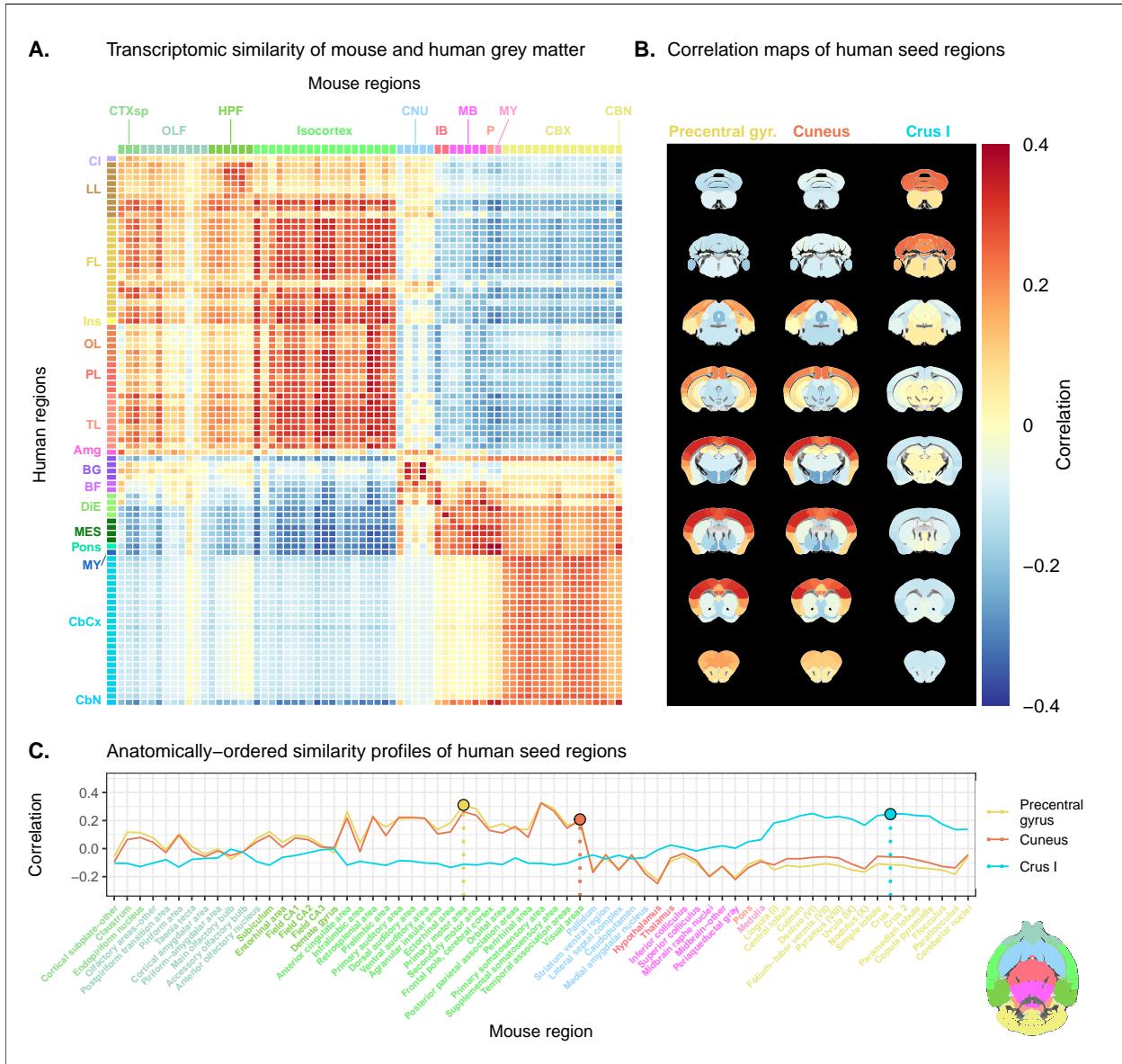


Figure 1. Transcriptomic similarity in the mouse and human brains. **(A)** Similarity matrix displaying the correlation between 67 mouse regions and 88 human regions based on the expression of 2835 homologous genes. Columns are annotated with 11 broad mouse regions: Cortical subplate (CTXsp), olfactory areas (OLF), hippocampal formation (HPF), isocortex, cerebral nuclei (CNU), interbrain (IB), midbrain (MB), pons (P), medulla (MY), cerebellar cortex (CBX), cerebellar nuclei (CBN). Rows are annotated with 16 broad human regions: Claustrum (CL), limbic lobe (LL), frontal lobe (FL), insula (Ins), occipital lobe (OL), parietal lobe (PL), temporal lobe (TL), amygdala (Amg), basal ganglia (BG), basal forebrain (BF), diencephalon (DIE), mesencephalon (MES), pons, myelencephalon (MY), cerebellar cortex (CbCx), cerebellar nuclei (CbN). Broad patterns of similarity are evident between coarsely defined brain regions, while correlation patterns are mostly homogeneous within these regions. **(B)** Mouse brain coronal slices showing similarity profiles for the human precentral gyrus, cuneus and crus I. Correlation patterns for the precentral gyrus and cuneus are highly similar to one another and broadly similar to most isocortical regions. The crus I is homogeneously similar to the mouse cerebellum. **(C)** Anatomically-ordered line charts displaying the similarity profiles for the seed regions in (B). Dashed vertical lines indicate the canonical mouse homologue for each human seed. Annotation colours correspond to atlas colours from the AMBA and AHBA for mouse and human regions respectively.

152 distinctiveness of the expression profiles.

153 The approach used in the previous analysis relied on using homologous genes as a common space between
154 the mouse and human brain. This approach effectively assigns equal value to each gene, whereas a more
155 powerful approach would be to weight genes by their ability to distinguish between different brain regions.
156 We investigated whether we could accomplish this by constructing a new set of variables from combinations
157 of the homologous genes. Our primary goal here was to transform the initial gene space into a new common
158 space that would improve the locality of the matches. However while we sought a transformation that would
159 allow us to recapitulate known mouse-human neuroanatomical homologues, we also wanted to avoid directly
160 encoding such correspondences in the transformation. Using this information as part of the optimization
161 process for the transformation would run the risk of driving the transformation towards mouse-human pairs
162 that are already known. While we are interested in being able to recover such matches, we are equally
163 interested in identifying novel and unexpected associations between neuroanatomical regions in the mouse
164 and human brains (e.g. one-to-many correspondences). Given these criteria, our approach to identifying an
165 appropriate transformation was to train a multi-layer perceptron classifier on the data from the AMBA. The
166 classifier was tasked with predicting the 67 labels in our mouse atlas from the voxel-wise expression of the
167 homologous genes (Figure 2A).

168 While the model could have been trained using the data from either species, we chose to use the mouse
169 data because it provides continuous coverage of the entire brain and is thus better suited to this purpose.
170 In training the model to perform this classification task, we effectively optimize the network architecture
171 to identify a transformation from the input gene space to a space that encodes information about the
172 delineation between mouse brain regions. To extract this transformation, we removed the output layer from
173 the trained neural network. The resulting architecture defines a transformation from the input space to
174 a lower-dimensional gene expression latent space. We then applied this transformation to the mouse and
175 human gene-by-region expression matrices to obtain representations of the data in the latent common space
176 (Figure 2B). Finally, we used these gene expression latent common space matrices to compute the new
177 similarity matrix (Figure 2C). Since the optimization algorithm used to train the perceptron features an
178 inherent degree of stochasticity, we repeated this training and transformation process 500 times to generate
179 a distribution of latent spaces and similarity matrices over training runs. Although the neural network and
180 associated latent space do not directly provide information about which genes are most important for the
181 classification of specific mouse atlas labels, this type of information can be derived from the model using
182 attribution methods such as integrated gradients (Figure 2-figure supplement 1) (Sundararajan et al., 2017).
183 Each brain region in the classification task is associated with the input genes in different ways, such that

184 there isn't a single weighting of gene importance for the entire model. While most genes contribute to the
 185 classification of any given label in some capacity, it is often the case that the network relies on a reduced
 186 subset of genes to arrive at a decision. For example, the genes *Prrg2* and *Rgs2* were found to be most
 187 influential for the classification of the caudoputamen, when the feature attributions were averaged over all
 188 training runs. In contrast, *Rfx4* and *Tnncl* were the most influential for the classification of the primary
 189 motor area. In some cases, the spatial expression pattern of the gene clearly shows a demarcation of the
 190 region of interest (e.g. *Rgs2*), but this is not always the case, nor is it necessary, as the network learns from
 191 the entire gene expression signature of all voxels.

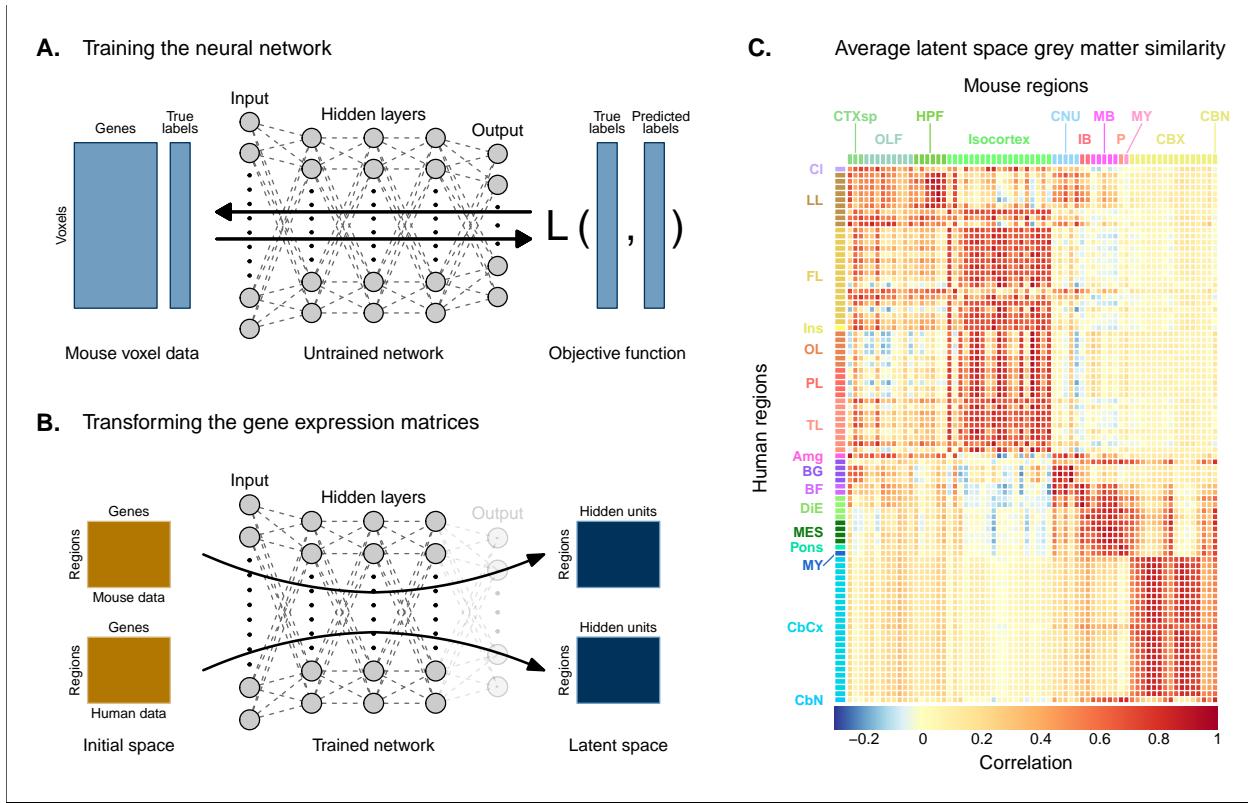


Figure 2. Creating a new common space. **(A)** Voxel-wise expression maps from 2835 homologous genes in the AMBA were used to train the neural network to classify each mouse voxel into one of 67 atlas regions. **(B)** Once the network is trained, the output layer is removed. The mouse and human regional gene expression matrices are passed through the network, resulting in lower-dimensional latent space representations of the data. The training and transformation process was repeated 500 times. **(C)** A similarity matrix displaying the gene expression latent space correlation between mouse and human regions, averaged over 500 neural network training runs. Similar brain regions exhibit very high correlation values. Column and row annotations as described in Figure 1.

192 To assess whether the latent space representations of the data improved the resolution of the mouse-human
 193 matches, we considered two criteria. The first was whether the similarity profiles of the mouse atlas regions
 194 were more localized within the corresponding broad regions of interest (e.g. primary motor area within
 195 isocortex), compared with their similarity profiles in the original gene space. We term this the locality
 196 criterion. The second criterion was whether the degree of similarity between canonical neuroanatomical
 197 homologues improved in this new latent common space. We term this the homology criterion. The locality

198 criterion tells us about our ability to extract finer-scale signal in these profiles, while the homology criterion
199 informs us about our ability to recover expected matches in this finer-scale signal. To evaluate these criteria,
200 we computed ranked similarity profiles for every region in the mouse brain, ordered such that a rank of 1
201 indicates the most similar human region. In addition, given the difference in absolute value between the
202 input gene space and gene expression latent space correlations, we scaled the similarity profiles to the interval
203 [0, 1] in order to make comparisons between the spaces.

204 We evaluated the locality criterion by examining the decay rate of the top of the similarity profiles. We
205 reasoned that the plateau of similarity to a broad brain region, as seen in the anatomically-ordered similarity
206 matrices and profiles (Figure 1, A and C; Figure 2C), would correspond to a similar plateau at the head of
207 the rank-ordered profiles. Moreover, the emergence of local signal would manifest as an increase in the range
208 between the peaks and troughs within the broad region. In the rank-ordered profiles, this would correspond
209 to a faster rate of decay at the head of the profile. In order to quantify this decay, we computed the rank
210 at which each region's similarity profile decreased to a scaled value of 0.75. This was calculated for every
211 mouse region in the initial gene space, as well as in each of the 500 gene expression latent spaces. As a
212 measurement of performance between the two representations of the data, we then took the difference in this
213 rank between each of the latent spaces and the original gene space (Figure 3A). A negative rank difference
214 indicates an improvement in the latent space.

215 Examining the structure-wise distributions of these rank differences, we found that for the majority of regions
216 in our mouse atlas, the classification approach resulted in either an improvement in the amount of locality
217 within a broad region, or no difference from the original gene space (Figure 3, B and C). We quantified the
218 improvement overall by fitting a logistic regression model with no predictors to the mean rank differences
219 of each of the atlas regions. We considered the success condition for the Bernoulli trials to be a mean rank
220 difference less than or equal to zero. The model estimate for the Bernoulli probability was $p = 0.78$ with a
221 95% confidence interval of [0.66, 0.86]. In other words, 52 of the 67 brain regions saw an improvement on
222 average when using the latent spaces. We additionally evaluated the same kind of logistic regression on a
223 region-wise basis to quantify how often the latent spaces resulted in an improvement for individual brain
224 regions (Figure 3C). We found that for 49 regions (73%), the model estimated the probability to be at least
225 at high as $p = 0.95$. While confidence intervals varied around this estimate, the range between the upper
226 and lower bound was only ever as high as 0.04. Thus these estimates are much higher than the expected
227 null probability of $p = 0.50$. A few regions performed worse in the latent spaces, notably the dentate gyrus
228 ($p = 0.0$, no variance), the thalamus ($p = 0.0020$, 95% CI [0.0003, 0.0146]), and the lateral septal complex
229 ($p = 0.004$, 95% CI [0.001, 0.016]). Beyond this binary measure of improvement, some regions exhibited a

230 large range of differences in rank over the various latent spaces. In particular regions like the main olfactory
231 bulb (mean rank difference of $\mu = 7$, 95% CI $[-12, 27]$) and accessory olfactory bulb $\mu = -3$, 95% CI
232 $[-27, 22]$) exhibit a substantial degree of variance. Other than these two areas, regions within the olfactory
233 areas (e.g. piriform area) were among those that benefited the most from the classification approach, showing
234 improvement in all sampled latent spaces. While the effects, i.e. rank differences, are smaller, the similarity
235 profiles of regions belonging to the isocortex and cerebellar cortex also saw an improvement in locality. All
236 models for isocortical areas returned probability estimates greater than $p = 0.95$. Moreover, 13 of the 19
237 isocortical regions were improved in all latent spaces. Brain regions belonging to the cerebellar cortex saw
238 similar improvement. In contrast, regions belonging to the cerebral nuclei, the diencephalon, midbrain and
239 hindbrain did not see much improvement in this new common space, with an average probability estimate of
240 $p = 0.36$ for this subset. For many such regions the degree of locality appears to be worse in this space, though
241 only by a small number of ranks, e.g. striatum ventral region (mean rank difference of $\mu = 2$, 95% CI $[-1, 5]$)
242 and lateral septal complex ($\mu = 6$, 95% CI $[2, 10]$). Indeed, computing the average rank difference over this
243 subset of regions across all latent spaces, we find $\mu = 2$ with 95% confidence interval $[-3, 6]$. These results
244 demonstrate that the supervised learning approach used here can improve the resolution of neuroanatomical
245 correspondences between the mouse and human brains, though the amount of improvement varies over the
246 brain. Regions that were already well-characterized using the initial set of homologous genes (e.g. subcortical
247 regions) did not benefit tremendously, but numerous regions in the cortical plate and subplate, as well as
248 the cerebellum, saw an improvement in locality in this new common space.

249 While the supervised learning approach improved our ability to identify matches on a finer scale for a number
250 of brain regions, this does not necessarily mean that those improved matches are biologically meaningful. The
251 second criterion for evaluating the performance of the neural network addresses whether this improvement
252 in locality captures what we would expect in terms of known mouse-human homologies. To this end, we
253 examined the degree of similarity between established mouse-human neuroanatomical pairs, both in the
254 initial gene expression space and in the set of latent spaces. We began by establishing a list of 36 canonical
255 mouse-human homologous pairs on the basis of common neuroanatomical labels in our atlases. For each of
256 these regions in the mouse brain, we compared the rank of the canonical human match in the rank-ordered
257 similarity profiles between the latent spaces and the original gene expression space (Figure 4A). The lower
258 the rank, the more similar the canonical pair, with a rank of 1 indicating maximal similarity. As described
259 above, we evaluated the overall performance of the classification approach by running a logistic regression
260 using the average latent space rank difference over all regions in our subset. Here we find an estimate
261 probability of $p = 0.58$ with 95% confidence interval $[0.42, 0.73]$. This is consistent with the null hypothetical

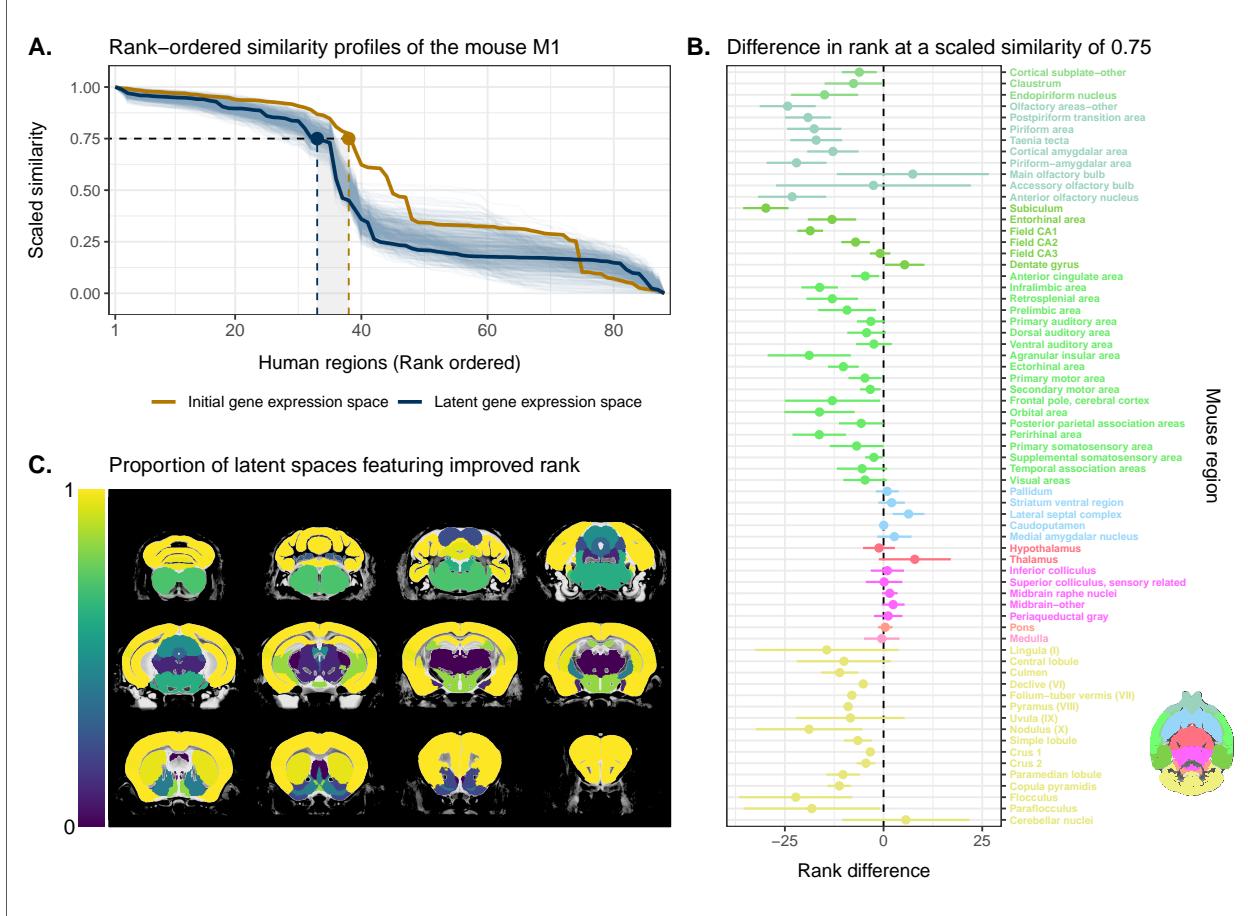


Figure 3. Quantifying improvement in locality in gene expression latent space. **(A)** The amount of local signal within a broadly similar region of the brain for a finer seed region's (e.g. primary motor area) similarity profile can be quantified by the decay rate of the head of the rank-ordered profile. Decay rate was quantified by computing the rank at a similarity of 0.75. This metric was compared between the initial gene expression space (orange line) and every gene expression latent space resulting from repeated training of the neural network (every blue line is a training outcome, heavy blue line serves as an example). A negative difference between these rank metrics indicates an improvement in locality in the latent space. **(B)** Structure-wise distributions of differences in rank at a similarity of 0.75 between the initial gene expression space and the gene expression latent spaces. Points and error bars represent mean and 95% confidence interval. Dashed black line at 0 indicates the threshold for improvement in one space over the other. Colours correspond to AMBA annotations as in Figures 1 and 2. Binomial likelihood (logistic regression) estimate of $p = 0.78$ with %95 CI [0.66, 0.86]. **(C)** Proportion of perceptron training runs resulting in an improvement or null difference in the gene expression latent space compared with the initial space, estimated using region-wise logistic regressions. Cortical and cerebellar regions exhibit high proportions of improvement, while subcortical regions are less likely to be improved by the classification process.

262 probability of $p = 0.5$. We also evaluated the model for each brain region and found that 21 of the 36 regions
263 (58%) return probability estimates of at least $p = 0.80$ (Figure 4B). We find pronounced improvement in
264 regions such as the piriform area, the subiculum, the primary motor and somatosensory areas, and the crus
265 2, all of which have an estimated probability of $p = 1$ with no variance around this value. A number of
266 regions also demonstrate improvement in a high proportion of latent spaces: the claustrum ($p = 0.89$, 95%
267 CI [0.86, 0.92]), the primary auditory area ($p = 0.88$, 95% CI [0.84, 0.90]), the visual areas ($p = 0.96$, 95%
268 CI [0.94, 0.98]), and the uvula ($p = 0.92$, 95% CI [0.89, 0.94]). Once again we find that many regions in
269 the sub-cortex do not benefit greatly from the gene expression latent spaces, since the initial gene set was
270 already recapitulating the appropriate match with maximal similarity. We find that the striatum ventral
271 region, hypothalamus, thalamus and caudoputamen are maximally similar to their canonical matches in
272 at least 90% of latent spaces. In such cases, the classification approach performs as well as the original
273 approach. While these probability estimates provide a sense of how often an improvement is returned, it is
274 important to note that many regions in this set exhibit a substantial degree of variance of the latent spaces
275 in the ranking of the canonical pairs, e.g. the claustrum (mean rank of $\mu = 13$, 95% CI [1, 35]), the visual
276 areas ($\mu = 23$, 95% CI [8, 37]), the paraflocculus ($\mu = 17$, 95% CI [1, 36]).

277 Finally, although many regions in the cerebellum feature some improvement in the latent spaces, the variation
278 in the rank of the standard human pair is often quite large, indicating some instability in the neural network's
279 ability to recover these matches. However, while the rank of the canonical pair varies in different instances of
280 the latent space, the top matches for any given cerebellar region are always cerebellar regions. For instance,
281 when the mouse crus 1 is used as the seed region, the human crus 1 is most often assigned a rank between 6
282 and 9. However, similar proportions in that range occur for the crus 2 and lobules V, VI and VIIIB, indicating
283 that these cerebellar regions are swapping ranks in the different latent spaces. Thus while cerebellar regions
284 are reliably associated with other cerebellar regions in the gene expression latent spaces, these associations
285 are not stable over multiple training runs.

286 Together, these results demonstrate that the multi-layer perceptron classification approach improves our abil-
287 ity to resolve finer scale mouse-human neuroanatomical matches within the broadly similar regions obtained
288 using the initial gene expression space. By training a classifier to predict the atlas labels in one species, we
289 were able to generate a new common space that amplified the amount of local signal within broadly similar
290 regions while also improving our ability to recover known mouse-human neuroanatomical pairs.

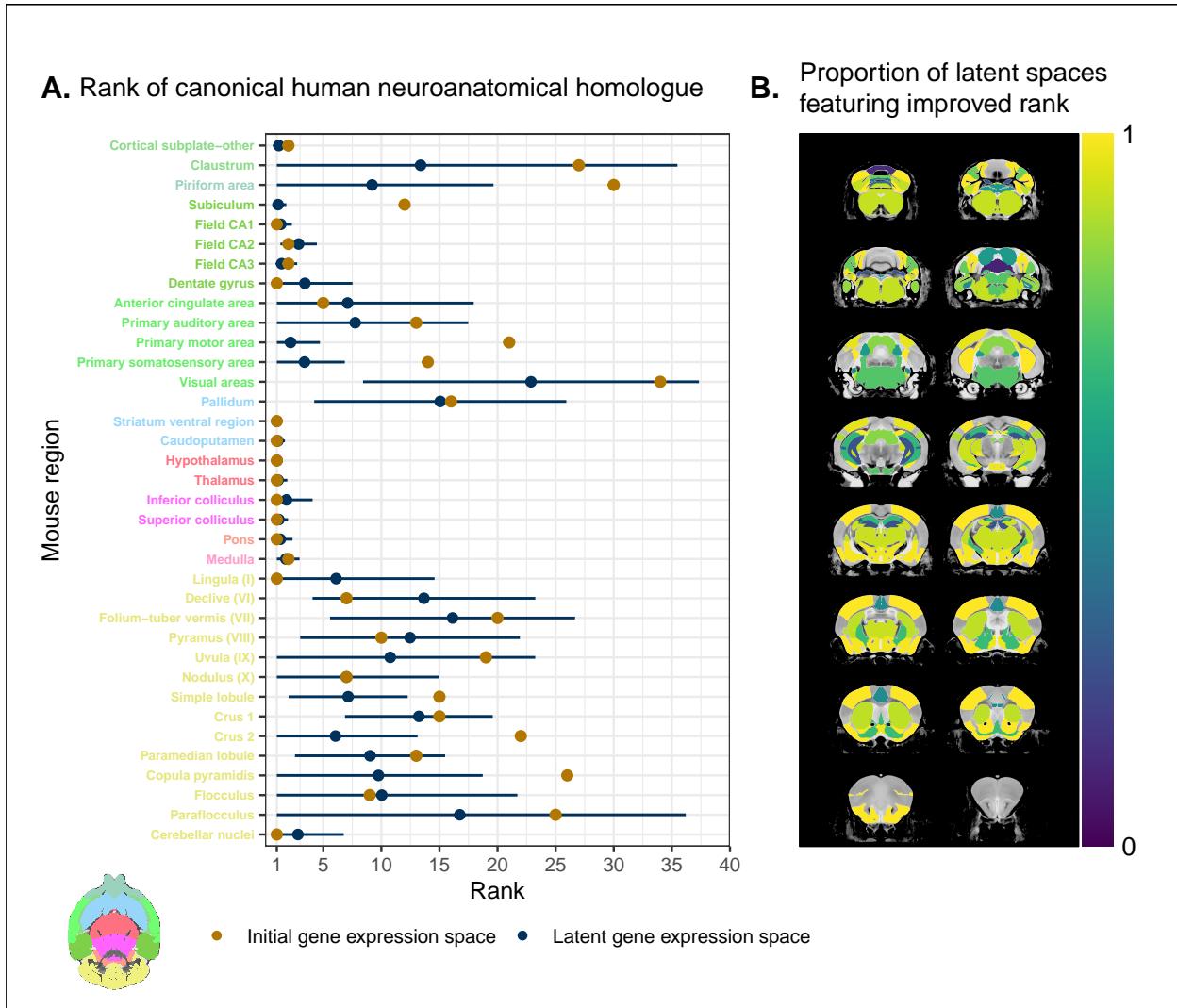


Figure 4. Recovering canonical neuroanatomical pairs in gene expression space. **(A)** Comparison between the ranks of canonical human matches for mouse seed regions between the initial gene expression space and gene expression latent spaces. Points and error bars represent mean and 95% confidence interval. Mouse region names are coloured according to the AMBA palette. **(B)** Proportion of latent spaces resulting in an improvement or null difference compared with the initial gene space. Uncoloured voxels correspond to regions with no established canonical human match.

²⁹¹ **Cortical areas involved in sensorimotor processing show greater transcriptomic**
²⁹² **similarity than supramodal areas**

²⁹³ It is well established that the brains of most, if not all, extant mammalian species follow a common organi-
²⁹⁴ zational blueprint inherited from an early mammalian ancestor (Kaas, 2011a). A number of cortical subdivi-
²⁹⁵ sions have consistently been identified in members of many distantly related mammalian species (Krubitzer,
²⁹⁶ 2007) and hypothesized to have been present in the common ancestor of all mammals (Kaas, 2011a). While
²⁹⁷ it is clear that basic sensorimotor cortical regions are found in the majority of mammals, including mice and
²⁹⁸ humans, there is much debate about the extent to which cortical areas involved in supramodal processing
²⁹⁹ are conserved across mammalian taxa. Although some supramodal regions were likely present in the earliest
³⁰⁰ mammals, including some cingulate regions and an orbitofrontal cortex (Kaas, 2011a), since the divergence
³⁰¹ of mouse and human lineages some 80 million years ago, the primate neocortex has undergone substantial
³⁰² expansion and re-organization (Kaas, 2012). Indeed, when comparing the human neocortex even to primate
³⁰³ model species, this is the likely locus of areas that cannot be easily translated between species (Rogier B.
³⁰⁴ Mars et al., 2018b). As a result, it is important to investigate whether our between-species mapping is more
³⁰⁵ successful in somatosensory areas than supramodal areas.

³⁰⁶ We assessed the similarity between mouse and human isocortical areas using the pairwise correlations in each
³⁰⁷ of the gene expression latent spaces returned from the multi-layer perceptron. For every region in the mouse
³⁰⁸ isocortex, we evaluated the distribution of maximal correlation values over latent spaces (Figure 5A). While
³⁰⁹ the region-wise variance for each isocortical area was large, we found that, on average, sensorimotor regions
³¹⁰ exhibited higher maximal correlation values than supramodal regions. The mouse primary somatosensory and
³¹¹ motor areas have the highest average maximal correlation values, with $r = 0.94 \pm 0.04$ and $r = 0.93 \pm 0.04$
³¹² respectively. We additionally examined the distributions of maximal correlation, grouped by cortex type
³¹³ (Figure 5B). To generate these distributions, we computed average maximal correlation values by cortex
³¹⁴ type in each of the latent spaces. Here too we find that sensorimotor regions are associated with higher
³¹⁵ maximal correlation values on average ($r = 0.89 \pm 0.04$), compared with supramodal areas ($r = 0.85 \pm 0.03$).
³¹⁶ These distributions demonstrate that sensorimotor isocortical regions exhibit more similarity overall on the
³¹⁷ basis of homologous gene expression than do supramodal regions.

³¹⁸ While we found that sensorimotor isocortical areas in the mouse brain were more similar to human brain
³¹⁹ regions than supramodal areas, the distributions of maximal correlation do not speak to the neuroanatomical
³²⁰ patterns of organization for these matches. To understand how the similarity patterns of mouse and human
³²¹ cortical subdivisions were organized, we used hierarchical clustering to cluster mouse and human isocortical

322 regions on the basis of their similarity profiles in the average gene expression latent space (Figure 5C). This
323 allows us to examine the similarity of regions to one another within and across brains at multiple levels
324 simultaneously.

325 At a high level, we find a striking segregation of the mouse isocortex into one main cluster that corresponds
326 to regions that are primarily engaged in sensorimotor processing and separate clusters of regions that are
327 supramodal. All of the sensorimotor areas cluster together, but three supramodal areas also form part of this
328 cluster: the retrosplenial area, the posterior parietal association areas, and the anterior cingulate cortex. Of
329 these, the retrosplenial area is the most different, being the first to separate out from the other regions. In
330 fact, the retrosplenial area is the mouse isocortical region with the smallest correlation values (Figure 5A).
331 The mouse sensorimotor cluster is characterized by high correlation values to human sensorimotor regions
332 like the precentral gyrus, the cuneus, and the postcentral gyrus, as well as low correlation values to the
333 piriform cortex and paraterminal gyrus.

334 At this level of clustering, the remaining mouse supramodal subdivisions form two clusters. These both
335 exhibit low similarity to the human somatosensory and visual areas, but the cluster containing the infral-
336 imbic and perirhinal areas additionally exhibits low correlation values with the precentral gyrus, anterior
337 paracentral lobule, and transverse gyri. The human cortical regions do not segregate as cleanly into senso-
338 rimotor and supramodal clusters. Under a similar level of description of four clusters of areas, the majority
339 of areas belong to a large cluster that includes a mix of cortical types. However, at a lower level of the
340 hierarchy, if the number of clusters is increased to five, this large cluster breaks up into two smaller clusters
341 that feature some delineation between supramodal and sensorimotor areas, which are primarily motor and
342 auditory in nature (e.g. precentral gyrus, Heschl's gyrus). Interestingly, the postcentral gyrus, i.e. primary
343 somatosensory area, forms a separate cluster with a set of visual areas such as the cuneus and lingual gyrus.
344 These regions exhibit very similar correlation profiles to the mouse isocortical regions, including maximal
345 correlation to the mouse primary somatosensory area, with an average of $r = 0.92$. The cluster is character-
346 ized by high correlations to the mouse sensorimotor cluster and low correlations to the mouse supramodal
347 clusters. Overall the human sensorimotor isocortical regions are loosely organized in clusters that contain
348 sensory-visual areas and auditory-motor areas.

349 We additionally ran hierarchical clustering on the isocortical similarity matrix in the original homologous
350 gene space. While the cluster annotations were not substantially different in this space, we observed that
351 the Euclidean distances within and between clusters were smaller compared with the latent space clustering,
352 further confirming that the perceptron classification approach improves the segregation of brain regions in
353 the gene expression common space (Figure 5D).

Overall, we observe a greater degree of similarity between mouse and human cortical regions involved in basic sensorimotor processing compared with supramodal or association areas. This is in line with the large body of existing research that suggests that sensory and motor areas of the cortex are conserved across the brains of mammals. While sensorimotor areas exhibit a greater degree of similarity than supramodal areas, the neuroanatomical pattern of correspondences obtained using mouse-human homologous genes is not at the level of individual cortical areas. Still, using a clustering approach we identified clear distinctions in the patterns of similarity between sensorimotor and supramodal areas, especially for regions in the mouse isocortex.

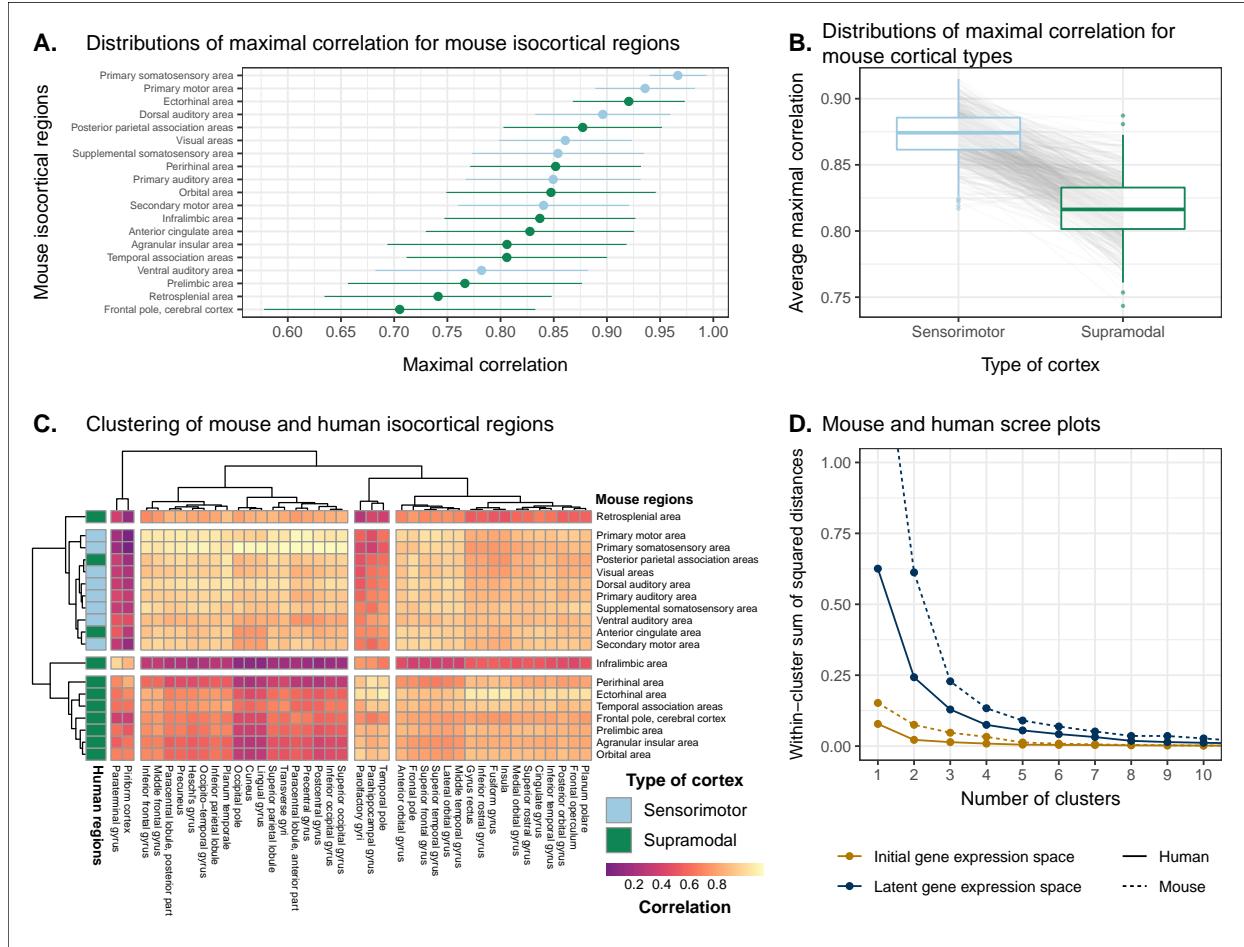


Figure 5. Similarity of mouse-human isocortical regions. **(A)** Maximal correlation distributions of mouse isocortical regions. Points and error bars represent mean and 95% confidence interval over latent space samples. **(B)** Distributions of average maximal correlation for sensorimotor and supramodal isocortical areas in each gene expression latent space. Grey lines correspond to individual latent spaces. **(C)** Hierarchical clustering of mouse and human isocortical regions based on average latent space correlation values. Mouse regions are annotated as sensorimotor or supramodal. Four clusters were chosen for visualization using the elbow method. **(D)** Within-cluster sum of squared distances for different numbers of mouse and human isocortical clusters in the average latent space and initial homologous gene space.

362 **Transcriptomic comparison of the mouse and human striatum**

363 We have focused here on comparing mouse and human brain organization using transcriptomic data, with
364 a latent space based on homologous genes as the common space between the two species. To date, common
365 space comparisons between the mouse and human brain have only been performed using functional con-
366 nectivity (Balsters et al., 2020; Schaeffer et al., 2020). As a case in point, Balsters et al. (2020) compared
367 mouse and human striatal organization using this measure. They found that the nucleus accumbens was
368 highly conserved between mice and humans, and that voxels in the posterior part of the human putamen
369 were significantly similar to the lateral portion of their mouse caudoputamen parcellation. Additionally,
370 they report that 85% of voxels in the human striatum were not significantly similar to any of their mouse
371 striatal seeds, and that 25% of human striatal voxels were significantly dissimilar compared with the mouse.
372 These differences were understandable, as they involved parts of the human striatum that connected to parts
373 of prefrontal cortex that have no known homolog in the mouse (Neubert et al., 2014). However, it is not
374 necessarily the case that between-species differences in connectivity are associated with distinct architectonic
375 or molecular signatures. Therefore, we investigated the patterns of similarity between the mouse and human
376 striata on the basis of gene expression using the neural network latent space representations.

377 We first identified the striatal regions present in the Allen human dataset: the caudate, the putamen, and the
378 nucleus accumbens. We evaluated the correlation between the microarray samples in these regions and every
379 region in the mouse atlas. Based on these correlation values, we focused our analysis on the four mouse
380 regions that were consistently the most similar across all latent spaces: the caudoputamen, the nucleus
381 accumbens, the fundus of striatum, and the olfactory tubercle. For each of the human striatal regions, we
382 then calculated the average correlation over the samples to each of the mouse targets. We examined the
383 distribution of these average correlation values over the latent spaces (Figure 6A). We find that the human
384 caudate and putamen consistently exhibit the strongest degree of similarity to the mouse caudoputamen.
385 The median of the distribution for the caudate-caudoputamen pairs is 0.95 and 0.97 for the putamen-
386 caudoputamen pairs, with modal values of 0.94 and 0.97, respectively. All latent spaces return correlations
387 greater than 0.9 for caudate-caudoputamen and putamen-caudoputamen pairs. Beyond this expected top
388 match, the caudate and putamen both exhibit high similarity to the nucleus accumbens and the fundus of
389 striatum, with mean correlation values of about 0.80. Neither of these target regions is consistently more
390 similar to the mouse caudoputamen over all latent spaces.

391 While the similarity of the caudate and the putamen to the caudoputamen is unsurprising, the story is not
392 as clear for the human nucleus accumbens. We find that the variance in correlation calculated over all mouse

393 targets is much lower ($\sigma = 0.04$) compared with the equivalent variances for the caudate ($\sigma = 0.09$) and
394 putamen ($\sigma = 0.10$), indicating less specificity to any one mouse striatal target. In particular, the human
395 nucleus accumbens isn't as specifically similar to the mouse nucleus accumbens in the way that the caudate
396 and putamen are similar to the caudoputamen. The mouse target distributions are right-shifted compared
397 with those for the caudate and putamen, with mean values of 0.90, 0.89, and 0.89 for the mouse nucleus
398 accumbens, caudoputamen, and fundus of striatum, respectively. The human accumbens also exhibits a high
399 degree of similarity to the mouse olfactory tubercle, the distribution of which is also right-shifted compared
400 with the caudate and putamen.

401 Given the high correlation of the human caudate and putamen to the mouse caudoputamen, as well as the
402 finding reported by Balsters et al. about the similarity of the lateral caudoputamen to the putamen, we were
403 curious as to whether we could identify sub-regional patterns of similarity in the caudoputamen and other
404 striatal regions using these gene expression data. To probe this question, we first examined the average latent
405 space correlation between each voxel in the mouse striatum and every region in the human atlas. We created
406 brain maps for the human regions that exhibited the highest mean correlation values, averaged over mouse
407 striatal voxels: the caudate, the putamen, the nucleus accumbens, and the septal nuclei (Figure 6B). We find
408 that voxels in the caudoputamen exhibit a homogeneous pattern of similarity to both the caudate and the
409 putamen. On average, voxels in the caudoputamen have a correlation of 0.95 to the caudate and 0.94 to the
410 putamen, with standard deviations of 0.04 and 0.05 respectively. The caudate and putamen are associated
411 with correlations of at least 0.90 in 88% and 84% of caudoputamen voxels. A number of voxels are also
412 highly similar to the human nucleus accumbens, with an average correlation value of 0.90 and 55% of voxels
413 returning a correlation of at least 0.9. The caudoputamen voxels most similar to the nucleus accumbens lie
414 in the ventral-rostral part of the region. Of course, voxels in the mouse nucleus accumbens are also highly
415 similar to the human nucleus accumbens, with an average of 0.90 and standard deviation of 0.06. While the
416 human nucleus accumbens is the most strongly correlated region, a number of voxels also exhibit reasonably
417 strong correlations to the substantia innominata, the septal nuclei, and the amygdala. Indeed, 91% of voxels
418 in the accumbens are correlated at a value of 0.7 or higher to the substantia innominata. The equivalent
419 percentages for the septal nuclei and amygdala are 78% and 74% respectively.

420 We additionally examined the proportion of latent spaces in which each voxel in the mouse striatum was
421 maximally similar to the human target regions (Figure 6C). As expected, we find that voxels in the cau-
422 doputamen are most often maximally similar to the human caudate and putamen, with 75% of voxels in
423 the caudoputamen being maximally similar to the caudate or putamen in at least 95% of latent spaces, and
424 62% of voxels being maximally similar to one of those targets in all latent spaces. Interestingly, we observe

425 the emergence of a continuous bilateral pattern of specificity to the caudate and putamen, with voxels in
426 the rostral and lateral-caudal parts of the caudoputamen being more specific to the caudate, and voxels in
427 the medial-rostral part being more specific to the putamen. This map highlights subtle differences in the
428 similarity between caudoputamen voxels and the caudate or putamen. While this pattern distinguishes the
429 two regions on the basis of which is the top match, individual voxels have very similar correlation values to
430 the targets (Figure 6B), with a mean difference in correlation of only 0.006. Beyond the caudoputamen, we
431 find that the accumbens and olfactory tubercle in the mouse are consistently similar to the human nucleus
432 accumbens, with 80% of mouse accumbens voxels and 65% of olfactory tubercle voxels having the human
433 accumbens as their top match in at least 80% of latent spaces. For those voxels below this threshold, the
434 human regions that are most often the top match are once again the amygdala, the septal nuclei, and the
435 substantia innominata.

436 Overall, we observe a strong association between the mouse caudoputamen and both the human caudate and
437 putamen. While we find a subtle pattern of specificity to either region among voxels in the caudoputamen on
438 the basis of maximal similarity, the high degree of similarity in the correlation values to each region suggests
439 that the majority of voxels in the caudoputamen are equally similar to the caudate and the putamen on the
440 basis of the expression of mouse-human homologous genes. We also find that the nucleus accumbens is well
441 conserved across species. However the region also exhibits patterns of similarity that go beyond the simple
442 one-to-one match. The human accumbens features similar correlation values to the mouse caudoputamen
443 and fundus of striatum, in addition to the accumbens proper, with no sharp distinction between these regions.
444 It also exhibits a larger degree of similarity to the mouse olfactory tubercle. This is also seen in the mouse
445 striatum, where voxels in the accumbens and the olfactory tubercle map onto the human accumbens.

446 Discussion

447 We have demonstrated how spatial transcriptomic patterns of homologous genes can be used to make quan-
448 titative comparisons between the mouse and human brain. We showed that using homologous genes as a
449 common space allows one to easily identify coarse similarities in brain structures across species, but that
450 more fine-scaled parcellations, such as at the level of cortical areas, are more complex. Despite this limi-
451 tation, the approach still allows for a formal assessment of different patterns of between-species similarity
452 in primary compared to supramodal regions, identifications of distinct clusters of cortical territories across
453 species, and comparison of between-species similarities at the transcriptomic level to those observed using
454 other modalities. We will discuss our observations in the context of the importance of the mouse as a model

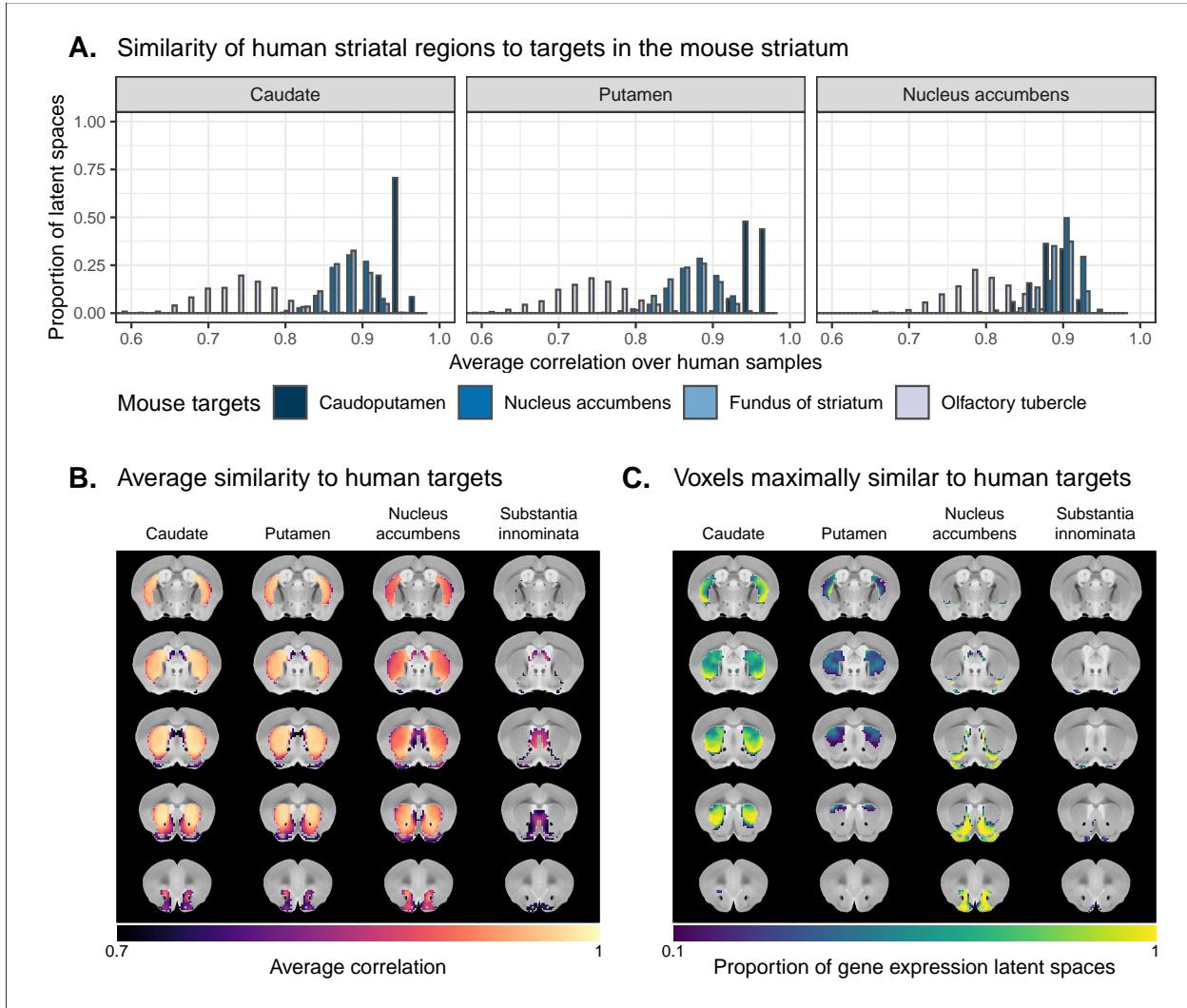


Figure 6. Similarity among mouse and human striatal regions. **(A)** Distributions over gene expression latent spaces of region-wise average correlation values for mouse and human striatal pairs. Human regions were chosen based on the AHBA ontology. Mouse target regions were chosen to be those with the highest average correlation values. **(B)** Latent space averaged correlations between voxels in the mouse striatum and human target regions. Target regions were selected based on the highest mean correlation across all striatal voxels. **(C)** Proportions of latent spaces in which mouse striatal voxels are maximally similar to human target regions.

455 for human neuroscience below.

456 The abundance of neuroscience research performed using mice has resulted in a wealth of knowledge about the
457 mouse brain. In the preclinical setting, mouse models are utilized with the intention of better understanding
458 human neuropathology. For instance, in the context of autism spectrum disorders, a plethora of studies
459 using mouse models have reported on the neurobiological and neuroanatomical phenotypes that arise from
460 mutations at specific genetic loci (Gompers et al., 2017; Horev et al., 2011; Pagani et al., 2021). It is common
461 for researchers involved in translational neuroscience to rely on findings of this kind to make inferences about
462 the human disorder. The typical approach, which is to identify rough post-hoc correspondences between
463 neuroanatomical ontologies, is not particularly comprehensive and is subject to confirmation bias. While it
464 may be a reasonable starting point for comparison, the true correspondence between the mouse and human
465 brain is likely more complicated given the evolutionary distance between the two species. Although overall
466 patterns of brain organization, including the general pattern of neocortical organization, are similar across
467 all mammals, substantial differences are evident (Ventura-Antunes et al., 2013). To make matters worse,
468 researchers from the different neuroscientific traditions often use distinct terminology, further complicating
469 detailed information exchange. To address these problems, we sought to establish a first quantitative whole-
470 brain comparison between the two species.

471 The expression of homologous genes provides an elegant way to define a common space for quantitative cross-
472 species comparisons since it relies on homology at a deep molecular biological level. The approach is not
473 without limitations however. First, the acquisition of whole-brain transcriptomic data is labour-intensive,
474 time consuming, and invasive. These data sets cannot be generated easily, especially in the human, in which
475 the process depends on the availability of post-mortem samples. As a result, the effective sample sizes are
476 extremely limited in this domain. For instance, in the Allen mouse coronal in-situ hybridization data set
477 used here, the brain-wide expression of each gene is sampled only once (barring a few exceptions). This
478 constrains the types of analyses that are possible (e.g. null hypothesis significance testing) and largely limits
479 the availability of replication data sets. That being said, new technologies, such as spatial transcriptomics,
480 are gradually making it easier to acquire brain-wide gene expression data in less time and at lower cost (Ortiz
481 et al., 2020; Stahl et al., 2016; Vickovic et al., 2019). Second, the approach of relying on all available genes
482 is subject to noise. To address this issue, Myers (2017) (Myers, 2017) used a method of gene set selection
483 to attempt to improve the correspondence between established mouse-human homologies. While this lead
484 to improvement, it was only at the level of coarsely defined regions (e.g. cortex-cortex). Our approach,
485 therefore, was to use supervised machine learning to create a latent common space based on combinations
486 of homologous genes that can delineate areas within a single species.

487 This latent common space approach led to a substantial improvement in specificity of between-species com-
488 parisons. Nevertheless, it is evident that the first major distinction in gene expression patterns within a
489 species, and the easiest identification of similarity across species, is at the coarse anatomical level of the
490 major subdivisions of the vertebrate brain, such as the isocortex, cerebellar hemispheres and nuclei, and
491 brain stem. All of these territories were present in the ancestral vertebrate brain (Striedter and Northcutt,
492 2020) and the ability to detect conserved transcriptomic signatures at this level is not surprising. Within
493 such structures, such as the isocortex, our ability to make simple one-to-one correspondences decreased. This
494 is partly because areas within a coarse structure have more similar transcriptomic profiles, but also likely
495 due to the fact that a single area in one brain does not have a single correspondent in another, larger brain.
496 In other words, regions in the brains of related species may exhibit one-to-many or many-to-many mappings.
497 In our study, we found greater cross-species similarity between cortical areas associated with sensorimotor
498 processing than areas in supramodal cortex. Primary areas, including the sensorimotor areas, are present
499 in all mammals studied to date and likely part of the common ancestors of all mammals (Kaas, 2011a;
500 Krubitzer, 2007). Although this common ancestor likely also had non-primary areas, it cannot be denied
501 that association cortex expanded dramatically in primates and especially so in the human brain (Chaplin et
502 al., 2013; Mars et al., 2016a). Again, the pattern found here of greater similarity in more conserved areas
503 might reflect this evolutionary history. In that context it is interesting to note that some non-primary areas
504 thought to be present in the common mammalian ancestor, such as cingulate and orbitofrontal cortex (Kaas,
505 2011a) showed relatively high correlation to human areas.

506 An advantage of the approach presented here is that it can, in principle, be applied to any aspect of brain
507 organization. Beyond simply establishing whether areas are similar across species in a particular common
508 space, comparing the results across common spaces established using different types of neuronal data can
509 inform on which larger principles of organization are similar across brains (Eichert et al., 2020). This is
510 illustrated here by the results of our striatal analysis. We found high similarity between the human caudate
511 and putamen and mouse caudoputamen, with little differentiation within these regions in a single species.
512 In contrast, Balsters et al. (2020) demonstrated that human caudoputamen contains a distinct pattern of
513 connectivity. At first sight, one could argue the results are in contrast. However, evolutionarily speaking, it
514 is quite probable that an overall similar transcriptomic signature of the striatum can be accompanied by a
515 distinct connectivity pattern to areas of the cortex present in only one of the two species. Indeed, this speaks
516 to the different types of similarity that can be studied, depending on which aspect of brain organization one
517 is interested in. Although the human brain is much larger than the mouse brain and contains a number
518 of cortical territories that have no homologue in the mouse brain (Kaas, 2011b; Rudebeck and Izquierdo,

519 2022), the similarity in transcriptomic signature mean that translations between the species is valid in many
520 contexts.

521 The power of a formal understanding of similarities and differences between brains at different levels of
522 organization is evident. In fundamental neuroscience, it will help translate results from data types that
523 cannot be obtained in humans to the human brain (Barron et al., 2021). In translational neuroscience, it
524 will, in a negative sense, help establish the limits of the translational paradigm by showing which aspects
525 of the human brain cannot be understood using the model species (Liu et al., 2021). In a positive sense,
526 it will also help by establishing and improving our understanding of the many aspects in which the model
527 and human brain do concur (Mandino et al., 2021). More ambitious still, it can provide a way in which
528 highly diverse manifestations of certain disease syndromes (e.g. autism spectrum disorder) (Grzadzinski et
529 al., 2013; Simonoff et al., 2008) and the availability of many distinct model strains (Ellegood et al., 2015),
530 each hypothesized to capture a distinct aspect of a multi-dimensional clinical syndrome, can be related to
531 one another. Ultimately, we believe that using the mapping of homologous gene expression between species
532 can be an important part of building a transform that maps information obtained using mice to humans and
533 vice versa.

534 Materials and methods

535 Mouse gene expression data

536 We used the adult mouse whole-brain in-situ hybridization data sets from the Allen Mouse Brain Atlas
537 (Lein et al., 2007). Specifically, we used 3D expression grid data, i.e. expression data aligned to the Allen
538 Mouse Brain Common Coordinate Framework (CCFv3)(Wang et al., 2020) and summarized under a grid
539 at a resolution of $200\mu\text{m}$. We downloaded the gene expression “energy” volumes from both the coronal
540 and sagittal in-situ hybridization experiments as a sequence of 32-bit float values using the Allen Institute’s
541 API (<http://help.brain-map.org/display/api/Downloading+3-D+Expression+Grid+Data>). These volumes
542 were subsequently reshaped into 3D images in the MINC format. Origin, extents, and spacing were defined
543 such that the image was RAS-oriented, with the origin at the point where the anterior commissure crosses
544 the midline. The MINC images from the coronal and sagittal data sets were then processed separately
545 using the Python programming language. The sagittal data set was first filtered to keep only those genes
546 that were also present in the coronal set. Images were imported using the `pyminc` package, masked and
547 reshaped to form an experiment-by-voxel expression matrix. We pre-processed this data by first applying a

548 `log2` transformation for consistency with the human data set. For those genes associated with more than
549 one in-situ hybridization experiment, we averaged the expression of each voxel across the experiments. We
550 subsequently filtered out genes for which more than 20% of voxels contained missing values. Finally, we
551 applied a K-nearest neighbours algorithm to impute the remaining missing values. The result of this pre-
552 processing pipeline was a gene-by-voxel expression matrix with 3958 genes and 61315 voxels for the coronal
553 data set and a matrix with 3619 genes and 26317 voxels for the sagittal data set.

554 Human gene expression data

555 Human gene expression data was obtained from the Allen Human Brain Atlas (Hawrylycz et al., 2012).
556 The data were downloaded from the Allen Institute’s API (<http://api.brain-map.org>) and pre-processed
557 using the `abagen` package in Python (<https://abagen.readthedocs.io/en/stable/>) (Arnatkeviciūtė et al., 2019;
558 Hawrylycz et al., 2012; Markello et al., 2021). We used the microarray data from the brains of all six donors,
559 each of which contains `log2` expression values for 58692 gene probes across numerous tissue samples. The
560 pre-processing pipeline included probe selection using differential stability on data from all donors and
561 intensity-based filtering of probes at a threshold of 0.5. The samples and genes were additionally normalized
562 for each donor individually using a scaled robust sigmoid function. In practice, this pipeline was implemented
563 using the `get_samples_in_mask` function from the `abagen` package. The remaining parameters were set to
564 their default values. The output of the pre-processing pipeline was a gene-by-sample expression matrix with
565 15627 genes and 3702 samples across all donors.

566 Mouse atlases

567 We used a version of the DSURQE atlas from the Mouse Imaging Centre (Dorr et al., 2008; Qiu et al., 2018;
568 Richards et al., 2011; Steadman et al., 2014; Ullmann et al., 2013), modified using the AMBA hierarchical
569 ontology, which was downloaded from the Allen Institute’s API. The labels of the DSURQE atlas correspond
570 to the leaf node regions in the AMBA ontology, which allowed us to use the hierarchical neuroanatomical
571 tree to aggregate and prune the atlas labels to the desired level of granularity. For the purposes of our
572 analyses, we removed white matter and ventricular regions entirely. The remaining grey matter regions were
573 aggregated up the hierarchy so that the majority of resulting labels contained enough voxels to be classified
574 appropriately by the multi-layer perceptron. In doing so, we maintained approximately the same level of
575 tree depth within a broad region (e.g. cerebellar regions were chosen at the same level of granularity). This
576 resulted in a mouse atlas with 67 grey matter regions. We additionally generated an atlas with 11 broader

577 regions for visualization and annotation purposes.

578 Human atlases

579 We used the hierarchical ontology from the AHBA, which we obtained using the Allen Institute’s API.
580 We aggregated and pruned the neuroanatomical hierarchy to correspond roughly to the level of granularity
581 obtained in our mouse atlas, resulting in 88 human brain regions. We additionally generated a set of 16
582 broad regions for visualization and annotation. White matter and ventricular regions were omitted entirely.

583 Regional expression and similarity matrices

584 We created the mouse and human gene-by-region expression matrices from the mouse gene-by-voxel and
585 human gene-by-sample expression matrices. First, we intersected the gene sets in these matrices with a
586 list of 3331 homologous genes obtained from the NCBI HomoloGene database (NCBI, 2018), resulting in
587 2835 homologous genes present in both the mouse and human expression matrices. We then annotated
588 each of the human samples with one of the 88 human atlas regions, and each of the mouse voxels with
589 one of the 67 mouse atlas regions, discarding white matter and ventricular entries in the process. These
590 labelled expression matrices were subsequently normalized as follows: For each matrix, we first standardized
591 every gene across all voxels/samples using a z-scoring procedure. We then centered every voxel/sample
592 by subtracting the average expression over all homologous genes. Finally, we generated the gene-by-region
593 expression matrices by averaging the expression of every gene over the voxels/samples corresponding to
594 each atlas region. Using these expression matrices, we generated the mouse-human similarity matrix by
595 computing the Pearson correlation coefficient between all pairs of mouse and human regions.

596 Gene enrichment analysis

597 We ran a gene enrichment analysis on the set of homologous genes obtained from the NCBI HomoloGene
598 database. We first downloaded Gene Ontology data for biological process related modules from the Bader
599 Lab at the University of Toronto (<http://baderlab.org/GeneSets>). These data include a gene set of 16563
600 genes and a module set of 15757 biological process modules. Every module is associated with a subset
601 of genes from the full gene set. For each module, we used a hypergeometric test to evaluate whether the
602 homologous gene set was over-represented in the module subset, compared with the full gene set. The
603 resulting p-values were adjusted for multiple comparisons using the false-discovery rate method (Benjamini

604 and Hochberg, 1995). A total of 938 modules were found to be significant at a threshold of 0.001. The
605 surviving modules were ordered according to their p-values and written out to a comma-separated values
606 data file (Supplementary File 1). This analysis was carried out using the `tmod` package in the R programming
607 language.

608 Multi-layer perceptron classification and latent space

609 To improve the resolution of mouse-human neuroanatomical matches, we performed a supervised learning
610 approach, wherein we trained a multi-layer perceptron neural network to classify 67 mouse atlas regions
611 from the expression values of 2835 homologous genes. We chose a model architecture in which each layer
612 of the network was fully connected to previous and subsequent layers. To optimize the hyperparameters,
613 we implemented an ad hoc cross-validation procedure that took into account the fact that the majority of
614 genes in the coronal AMBA data set are sampled only once over the entire mouse brain. The procedure
615 involved a combination of the coronal data set and the sagittal in-situ hybridization data sets. For the
616 sagittal data set, we used the expression matrix described above. However, we used a modified version
617 of the coronal expression matrix. This matrix was generated using the pipeline described above with the
618 following modifications: 1. We applied a *unilateral* brain mask to the coronal images since the sagittal data
619 is unilateral by construction, and 2. we did not aggregate the expression of multiple in-situ hybridization
620 experiments for those genes in the coronal set pertaining to more than one experiment. We then filtered
621 these experiment-by-voxel expression matrices according to the list of mouse-human homologous genes, as
622 well as the human sample expression matrix. We also annotated the voxels in each of the expression matrices
623 with one of the 67 regions in the mouse atlas. Our validation procedure then involved iterative construction
624 of training and validation sets by sampling gene experiments from either the coronal or sagittal matrices: For
625 every gene in the homologous set, we first determined whether that gene was associated with more than one
626 experiment in the coronal matrix. If this was the case, we randomly sampled one of those experiments for the
627 training set and one of the remaining experiments for the validation set. If the gene was associated with only
628 one experiment in the coronal set, we randomly sampled either the coronal or sagittal experiment for the
629 training set and the other for the validation set. Once the training and validation sets were generated, they
630 were normalized using the procedure described above. We then trained the neural network using the training
631 set and evaluated its performance on the validation set. Given that the construction of the training and
632 validation sets involved some stochasticity, we repeated this construction, training, and validation procedure
633 10 times for every combination of hyperparameters.

634 The hyperparameters that we optimized using this method were the number of hidden layers in the network,

635 the number of hidden units (i.e. neurons) per hidden layer, the dropout rate, and the amount weight decay.
636 The values we optimized over were as follows. We varied the number of hidden layers between 3 and 5. We
637 varied the number of hidden units between 100 and 1000 in increments of 100. For the dropout rate, we
638 examined values of 0, 0.25 and 0.50. For the amount of weight decay, we examined values of 10^{-6} and 10^{-5} .
639 We found that the best-performing model had 3 hidden layers, 200 neurons per layer, a dropout rate of 0,
640 and a weight decay value of 10^{-6} . This model returned an average classification accuracy of 0.926 on the
641 training sets and of 0.526 on the validation sets. Following validation, we used the optimal hyperparameters
642 to train the network on the full bilateral coronal voxel-wise expression matrix.

643 These models were implemented in Python using PyTorch via the `skorch` library (<https://skorch.readthedocs.io/en/stable/>). For both validation and training, the models were trained over 200 epochs
644 using a maximum learning rate of 10^{-5} . We used the `AdamW` optimization algorithm (Loshchilov and Hutter,
645 2019) and `OneCycleLR` learning rate scheduler policy. The activation function used in the forward pass
646 was the rectified linear unit (ReLU) and the loss function was the negative log-likelihood loss, which is the
647 default for the `NeuralNetClassifier` class in `skorch`.

648 We used the trained perceptron to generate the latent gene expression space. To extract the appropriate
649 transformation, we removed the predictive output layer and soft-max transformation from the network
650 architecture. The resulting architecture returns the 200 hidden units in the third hidden layer as the output
651 of the network. To create the latent space data representations, we applied this network to the mouse
652 and human gene-by-region expression matrices, transposed so that the genes were the input variables. The
653 resulting matrices have 200 columns corresponding to the hidden units and 67 (88) rows corresponding to
654 the mouse (human) regions. They describe each brain region's weight over the hidden units. To create the
655 similarity matrix, we calculated the Pearson correlation coefficient between all pairs of mouse and human
656 regions.

657 Given the stochasticity inherent in training the network (e.g. random weight initialization and stochas-
658 tic optimization), we repeated the training and transformation process 500 times using the same network
659 architecture and input data.

661 Multi-layer perceptron feature importance

662 (WRITE THIS)

663 **Quantifying improvement in gene expression latent spaces**

664 To quantify the improvement in the locality criterion, we used a logistic regression model to estimate the
665 probability that the rank difference was less than or equal to zero. To estimate the overall improvement
666 due to the latent spaces, we created a binary variable to encode whether the average rank difference over
667 latent spaces for each region met the success criterion. This variable was then used as our target in a
668 logistic regression with no regressors. Once the model was fit, we applied the logistic function to the
669 intercept parameter estimate to get the corresponding estimate for the Bernoulli probability p . This was
670 also applied to the bounds on the variance estimate for the intercept to get the corresponding confidence
671 interval. We additionally applied this approach on a region-wise basis to evaluate the likelihood of a region
672 seeing improvement in the latent spaces. This was implemented using the `glm` function from the `stats`
673 package in the R programming language.

674 **Data and code availability**

675 This manuscript and all figures were generated programmatically using R Markdown (<https://rmarkdown.rstudio.com>).
676 The Allen Mouse Brain Atlas and Allen Human
677 Brain Atlas data sets are openly accessible and can be downloaded from the Allen Institute's API (<http://api.brain-map.org>). All of the code and additional data needed to generate this analysis, including figures
678 and manuscript, is accessible at <https://github.com/abeaucha/MouseHumanTranscriptomicSimilarity/>.
679

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685 **Competing interests**

686 The authors declare that they have no competing interests.

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879 **Figure supplements**

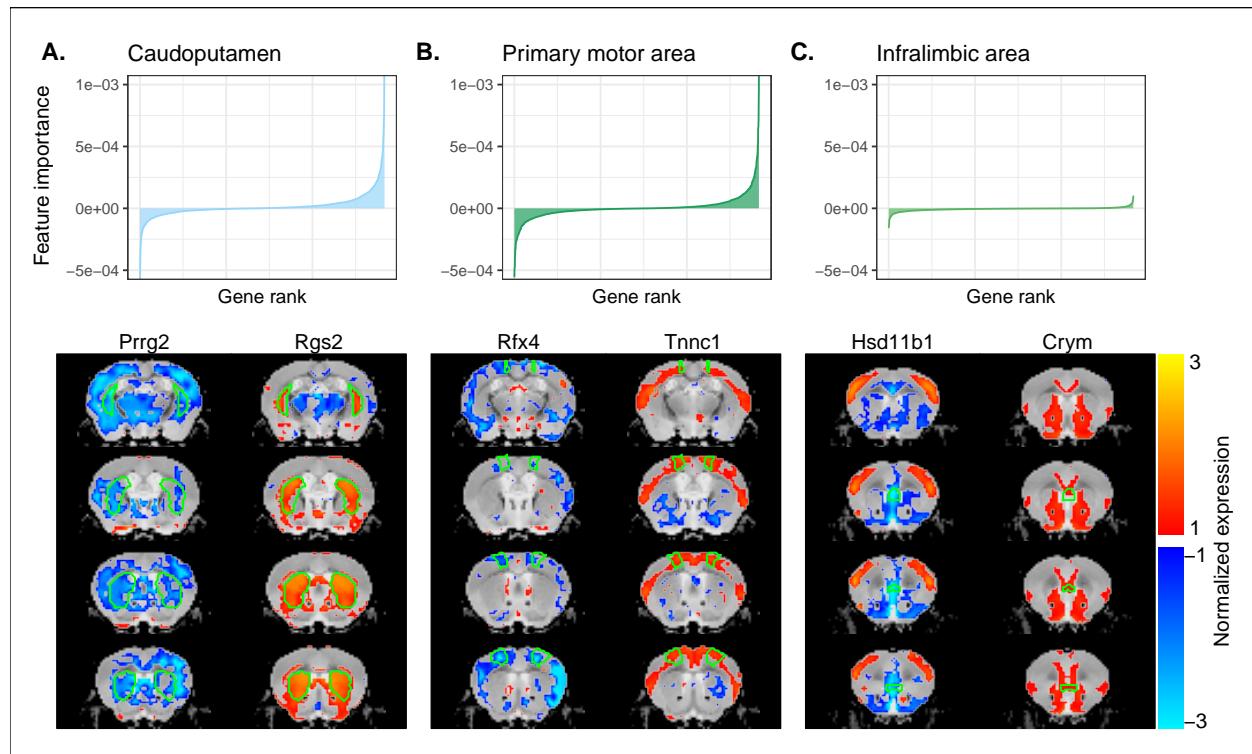


Figure 2-figure supplement 1. Multi-layer perceptron feature importance.