

¹ **Whole-brain comparison of rodent and human brains
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

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

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

Here we examine the patterns of similarity between the mouse and human brain using a common space constructed from spatial gene expression data sets. We begin with an initial set of 2835 homologous genes. Subsequently, we present and evaluate a novel method for improving the resolution of mouse-human neuroanatomical 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 ($r = 0.351$) as well as to brain stem structures like the pons
123 ($r = 0.328$ and $r = 0.335$ for the mouse and human nuclei respectively) and myelencephalon ($r = 0.288$ and
124 $r = 0.351$). 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 $r = 0.975$. 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 $r = 0.213$ and a standard deviation of $\sigma = 0.034$. Across
135 all regions, the variance of the correlations across cortical regions is $\sigma^2 = 0.0067$ while that across cerebellar
136 hemispheric regions is $\sigma^2 = 0.0013$, compared with a total variation of $\sigma^2 = 0.031$ 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

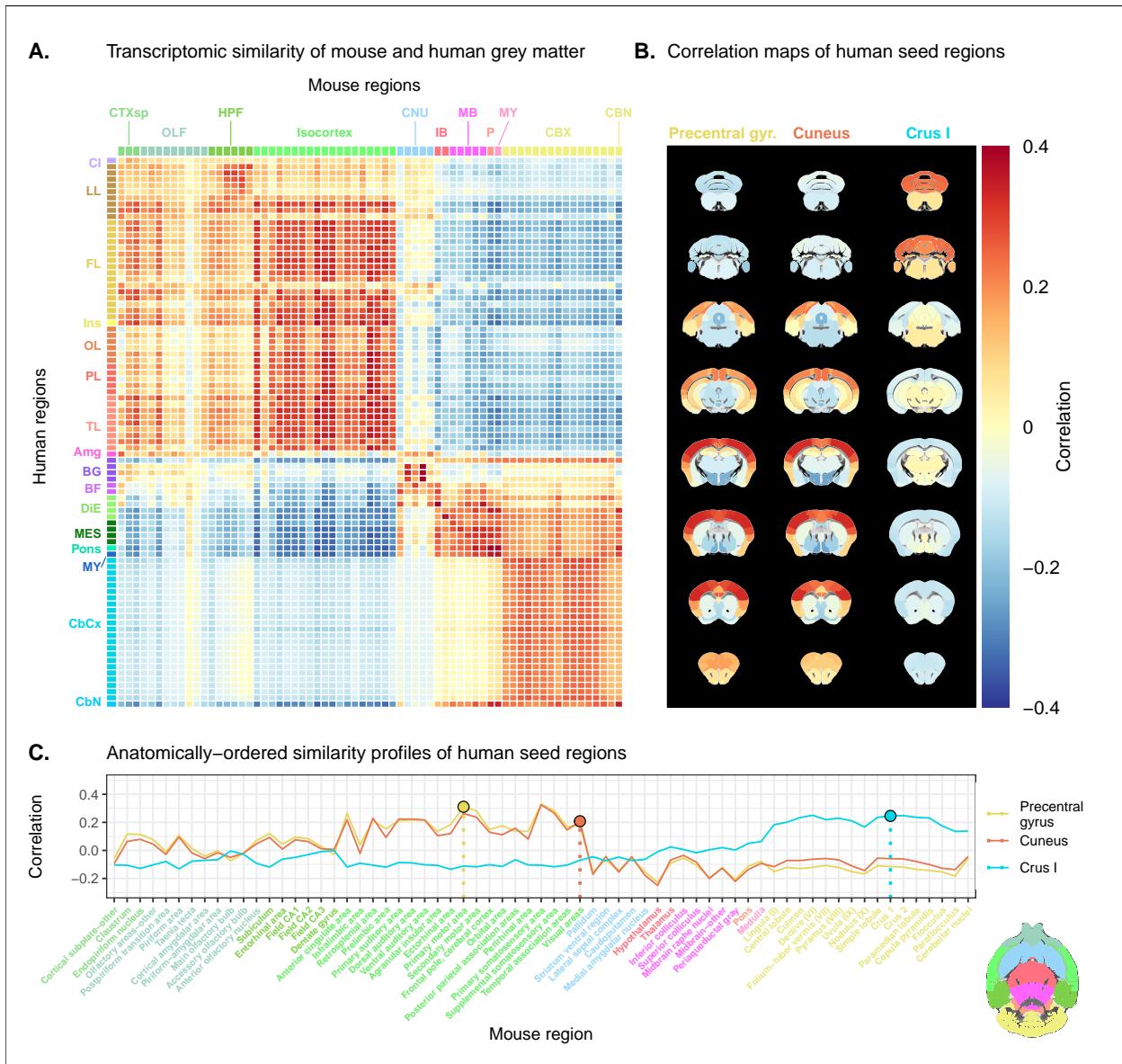


Figure 1. Transcriptomic similarity in the mouse and human brains. **(A)** Similarity matrix displaying the correlation between 67 mouse regions and 88 human regions based on the expression of 2835 homologous genes. Columns are annotated with 11 broad mouse regions: Cortical subplate (CTXsp), olfactory 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 *Cd4* 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 *Ghra3* 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. *Cd4*), 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.

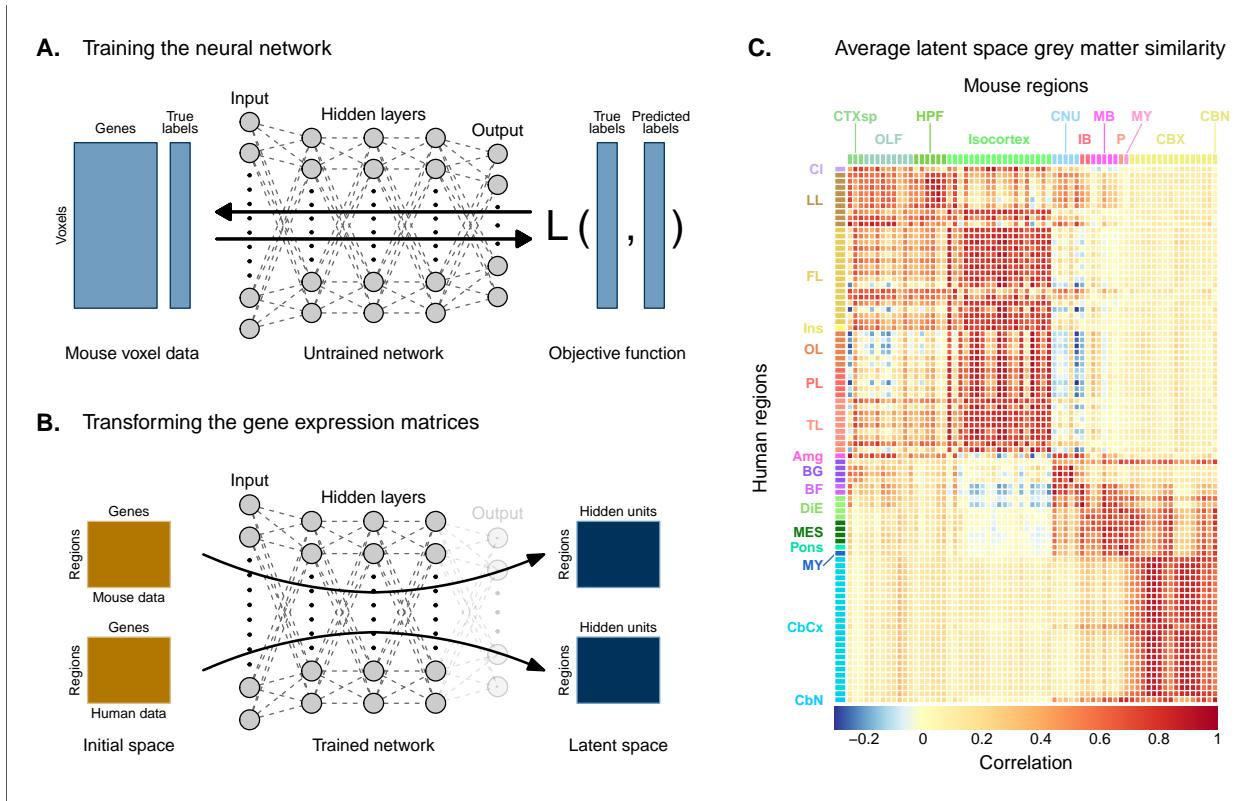


Figure 2. Creating a new common space. **(A)** Voxel-wise expression maps from 2835 homologous genes in the AMBA were used to train the neural network to classify each mouse voxel into one of 67 atlas regions. **(B)** Once the network is trained, the output layer is removed. The mouse and human regional 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 46 regions (69%), 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 and
226 lower bound was only ever as high as 0.04. Thus these estimates are higher than the expected null probability
227 of $p = 0.50$. A few regions performed worse in the latent spaces, notably the dentate gyrus ($p = 0.0$, no
228 variance), the striatum ventral region ($p = 0.016$, 95% CI [0.008, 0.032]), and the lateral septal complex
229 ($p = 0.016$, 95% CI [0.008, 0.032]). 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 $\mu = 10$, 95% CI $[-12, 33]$) and accessory olfactory bulb $\mu = 9$, 95% CI
232 $[-13, 31]$) 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 $p = 0.85$. Moreover, 9 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
240 of $p = 0.36$ for this subset. For many such regions the degree of locality appears to be worse in this space,
241 though only by a small number of ranks, e.g. striatum ventral region (mean rank difference of $\mu = 4$, 95% CI
242 $[1, 7]$) and lateral septal complex ($\mu = 6$, 95% CI $[0, 11]$). Indeed, computing the average rank difference over
243 this subset of regions across all latent spaces, we find $\mu = 2$ with 95% confidence interval $[-5, 8]$. 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 estimated
261 probability of $p = 0.64$ with 95% confidence interval $[0.47, 0.78]$. This is consistent with the null hypothetical

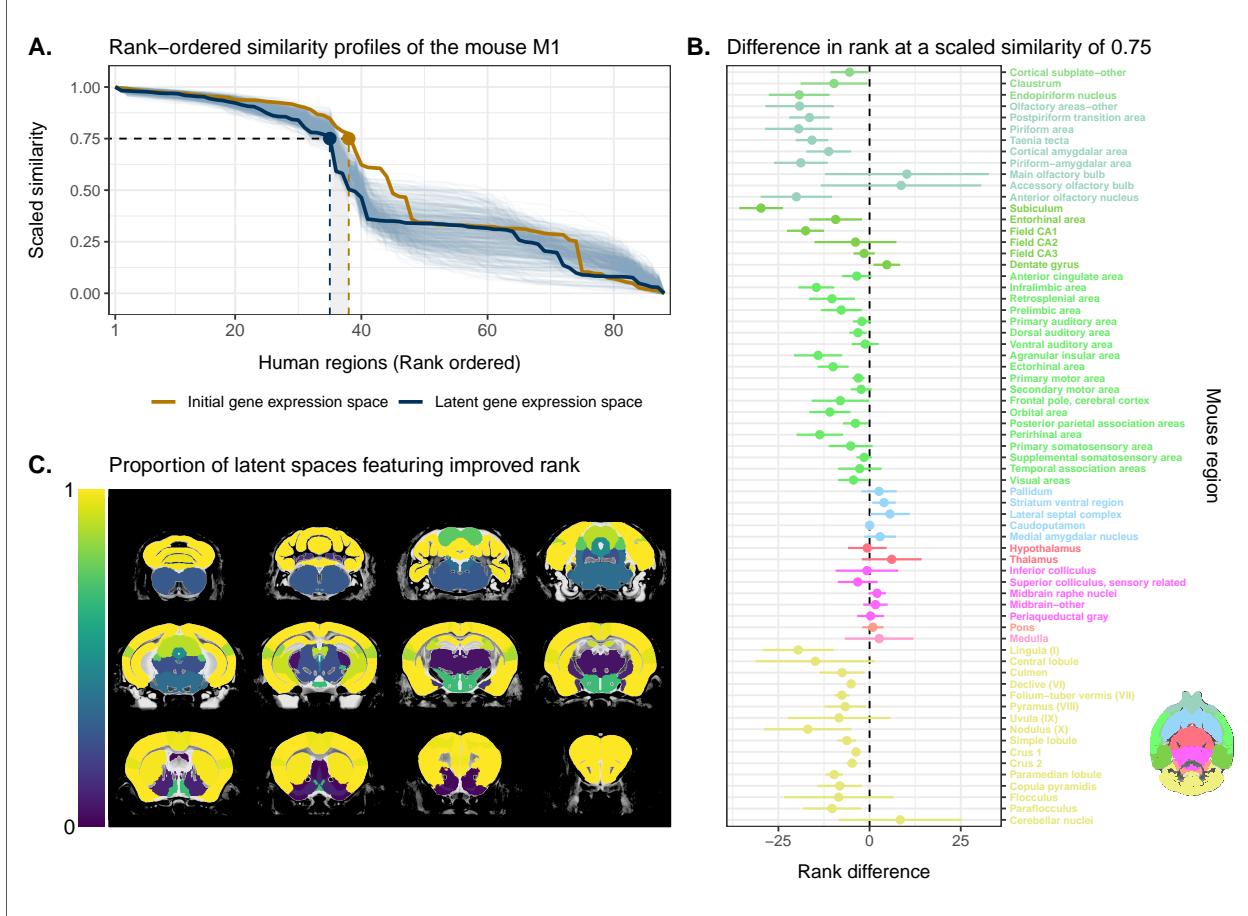


Figure 3. Quantifying improvement in locality in gene expression latent space. **(A)** The amount of local signal within a broadly similar region of the brain for a finer seed region's (e.g. primary motor area) similarity profile can be quantified by the decay rate of the head of the rank-ordered profile. 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 30 of the 36
263 regions (83%) return probability estimates of at least $p = 0.80$, with 24 regions (67%) returning estimates
264 of at least $p = 0.90$ (Figure 4B). We find pronounced improvement in regions such as the claustrum, the
265 piriform area, the primary motor and somatosensory areas, and the crus 2, all of which have an estimated
266 probability of $p = 1$ with no variance around this value. Additional examples of the many regions that
267 demonstrate improvement include: the primary auditory area ($p = 0.83$, 95% CI [0.80, 0.86]), the pallidum
268 ($p = 0.86$, 95% CI [0.83, 0.89]), and the crus 1 ($p = 0.92$, 95% CI [0.90, 0.94]). Once again we find that many
269 regions in the sub-cortex do not benefit greatly from the gene expression latent spaces, since the initial gene
270 set was already recapitulating the appropriate match with maximal similarity. We find that the striatum
271 ventral region, caudoputamen, hypothalamus, and pons are maximally similar to their canonical matches
272 in at least 95% 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
274 is important to note that many regions in this set exhibit a substantial degree of variance over the latent
275 spaces in the ranking of the canonical pairs, e.g. the primary auditory area ($\mu = 9$, 95% CI [1, 19]), the visual
276 areas ($\mu = 18$, 95% CI [7, 29]), the paraflocculus ($\mu = 16$, 95% CI [2, 29]). This is especially apparent for
277 cerebellar regions, indicating some instability in the neural network's ability to recover these matches.

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

283 **Cortical areas involved in sensorimotor processing show greater transcriptomic 284 similarity than supramodal areas**

285 It is well established that the brains of most, if not all, extant mammalian species follow a common organi-
286 zational blueprint inherited from an early mammalian ancestor (Kaas, 2011a). A number of cortical subdivi-
287 sions have consistently been identified in members of many distantly related mammalian species (Krubitzer,
288 2007) and hypothesized to have been present in the common ancestor of all mammals (Kaas, 2011a). While
289 it is clear that basic sensorimotor cortical regions are found in the majority of mammals, including mice and
290 humans, there is much debate about the extent to which cortical areas involved in supramodal processing
291 are conserved across mammalian taxa. Although some supramodal regions were likely present in the earliest

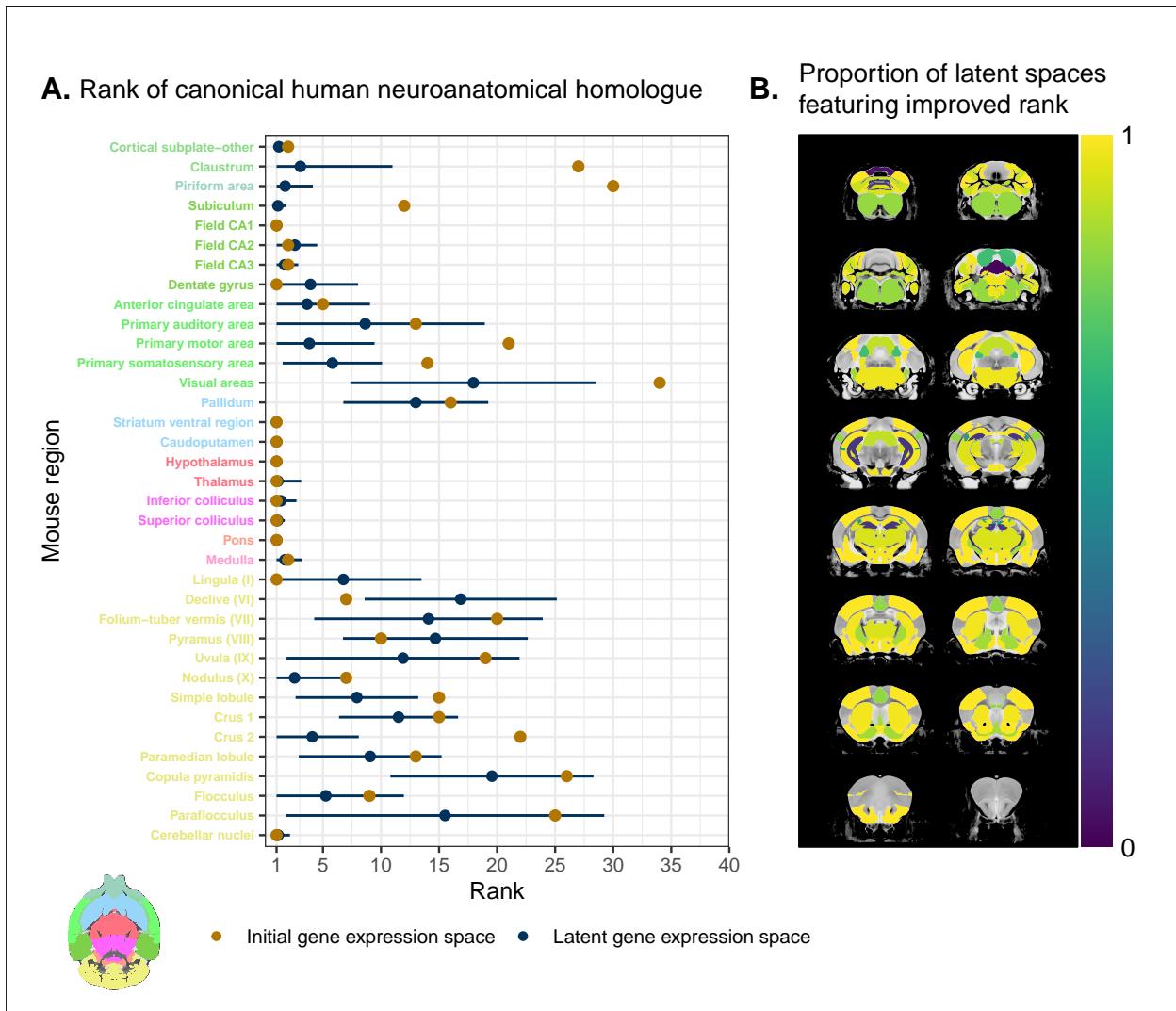


Figure 4. Recovering canonical neuroanatomical pairs in gene expression space. **(A)** Comparison between the ranks of canonical human matches for mouse seed regions between the initial gene expression space and gene expression latent spaces. Points and error bars represent mean and 95% confidence interval. Intervals are truncated at a minimal rank of 1, since values below this are meaningless. Mouse region names are coloured according to the AMBA palette. Binomial likelihood estimate of $p = 0.64$ with 95% CI [0.47, 0.78]. **(B)** Proportion of latent spaces resulting in an improvement or null difference compared with the initial gene space, estimated using region-wise logistic regressions. Uncoloured voxels correspond to regions with no established canonical human match.

292 mammals, including some cingulate regions and an orbitofrontal cortex (Kaas, 2011a), since the divergence
293 of mouse and human lineages some 80 million years ago, the primate neocortex has undergone substantial
294 expansion and re-organization (Kaas, 2012). Indeed, when comparing the human neocortex even to primate
295 model species, this is the likely locus of areas that cannot be easily translated between species (Rogier B.
296 Mars et al., 2018b). As a result, it is important to investigate whether our between-species mapping is more
297 successful in somatosensory areas than supramodal areas.

298 We assessed the similarity between mouse and human isocortical areas using the pairwise correlations in each
299 of the gene expression latent spaces returned from the multi-layer perceptron. For every region in the mouse
300 isocortex, we evaluated the distribution of maximal correlation values over latent spaces (Figure 5A). While
301 the region-wise variance for each isocortical area was large, we found that, on average, sensorimotor regions
302 exhibited higher maximal correlation values than supramodal regions (linear regression with binary predictor:
303 $t(17) = -1.854$, $p = 0.0812$). The mouse primary somatosensory ($r = 0.96$ with 95% CI [0.93, 0.98]) and
304 motor ($r = 0.95$ with 95% CI [0.92, 0.98]) areas have the highest average maximal correlation values. We
305 additionally examined the distributions of maximal correlation, grouped by cortex type (Figure 5B). To
306 generate these distributions, we computed average maximal correlation values by cortex type in each of the
307 latent spaces. Here too we find that sensorimotor regions are associated with higher maximal correlation
308 values on average compared with supramodal areas (linear mixed-effects regression: $t(499) = -49.9$, $p <$
309 $2 \cdot 10^{-16}$). These distributions demonstrate that sensorimotor isocortical regions exhibit more similarity
310 overall on the basis of homologous gene expression than do supramodal regions.

311 While we found that sensorimotor isocortical areas in the mouse brain were more similar to human brain
312 regions than supramodal areas, the distributions of maximal correlation do not speak to the neuroanatomical
313 patterns of organization for these matches. To understand how the similarity patterns of mouse and human
314 cortical subdivisions were organized, we used hierarchical clustering to cluster mouse and human isocortical
315 regions on the basis of their similarity profiles in the average gene expression latent space (Figure 5C). This
316 allows us to examine the similarity of regions to one another within and across brains at multiple levels
317 simultaneously.

318 At a high level, we find a striking segregation of the mouse isocortex into one main cluster that corresponds
319 to regions that are primarily engaged in sensorimotor processing and separate clusters of regions that are
320 supramodal. All of the sensorimotor areas cluster together, but two supramodal areas also form part of this
321 cluster: the posterior parietal association areas and the anterior cingulate cortex. The mouse sensorimotor
322 cluster is characterized by high correlation values to human sensorimotor regions like the precentral gyrus, the
323 cuneus, and the postcentral gyrus, as well as low correlation values to the piriform cortex and paraterminal

324 gyrus. At this level of clustering, the remaining mouse supramodal subdivisions form three clusters. The
325 retrosplenial area belongs to its own cluster, while the infralimbic and perirhinal areas cluster together.
326 The similarity profile of the retrosplenial area is most similar to the sensorimotor cluster, and these two
327 clusters are combined in the three-cluster solution. The remaining two mouse clusters are characterized by
328 low correlations to the human cluster containing sensorimotor areas. This is especially true for the cluster
329 containing the infralimbic and perirhinal areas.

330 On the human side, the four-cluster solution also features a sensorimotor cluster, which contains regions
331 like the pre- and post-central gyri, the cuneus, and Heschl's gyrus. This cluster exhibits a high degree
332 of similarity to the mouse sensorimotor cluster and low similarity to the mouse supramodal clusters. The
333 cortical regions not belonging to this cluster are split into three clusters. The majority of these remaining
334 regions form a large cluster that contains areas like the cingulate gyrus and the frontal pole. The parolfactory
335 gyri, parahippocampal gyrus and temporal pole form a separate cluster that exhibits high correlation to the
336 mouse ectorhinal, orbital, and prelimbic areas. Finally, the paraterminal gyrus and piriform cortex are
337 clustered together and exhibit high similarity to the mouse infralimbic area and low similarity to the mouse
338 sensorimotor cluster.

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

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

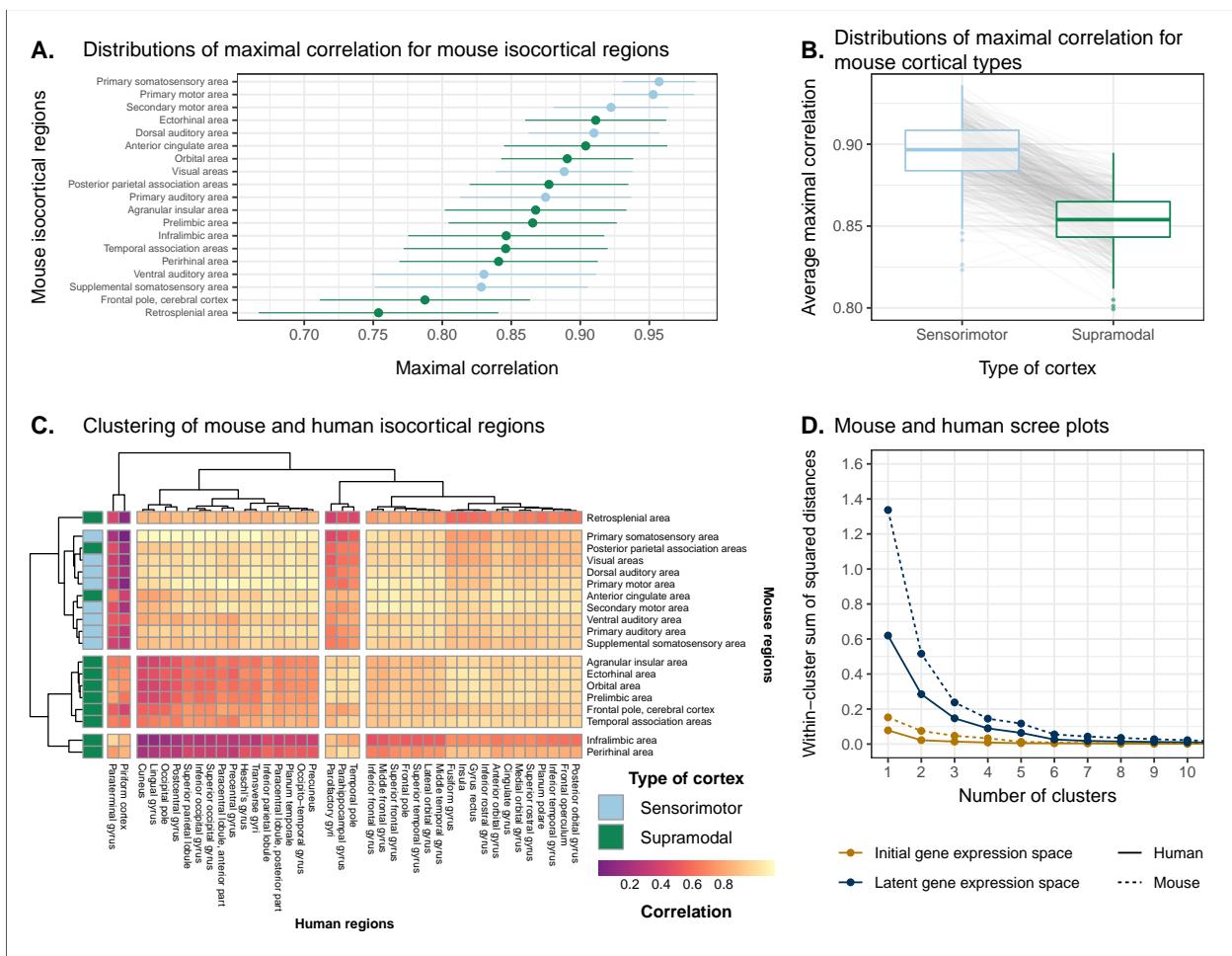


Figure 5. Similarity of mouse-human isocortical regions. (A) Maximal correlation distributions of mouse isocortical regions. Points and error bars represent mean and 95% confidence interval over latent space samples. Linear regression using average maximal correlation values: $t(17) = -1.854$, $p = 0.0812$. (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. Linear mixed-effects regression: $t(499) = -49.9$, $p < 2 \cdot 10^{-16}$. (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.

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

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

367 We first identified the striatal regions present in the Allen human dataset: the caudate, the putamen, and the
368 nucleus accumbens. We evaluated the correlation between the microarray samples in these regions and every
369 region in the mouse atlas. Based on these correlation values, we focused our analysis on the four mouse
370 regions that were consistently the most similar across all latent spaces: the caudoputamen, the nucleus
371 accumbens, the fundus of striatum, and the olfactory tubercle. For each of the human striatal regions, we
372 then calculated the average correlation over the samples to each of the mouse targets. We examined the
373 distribution of these average correlation values over the latent spaces (Figure 6A). We find that the human
374 caudate and putamen consistently exhibit the strongest degree of similarity to the mouse caudoputamen.
375 The median of the distributions for the caudate-caudoputamen pairs and putamen-caudoputamen pairs is
376 0.93, with modal values of 0.92 and 0.94, respectively. All latent spaces return correlations greater than
377 0.85 for caudate-caudoputamen and putamen-caudoputamen pairs. Beyond this expected top match, the
378 caudate and putamen both exhibit high similarity to the nucleus accumbens and the fundus of striatum,
379 with median correlation values of about 0.80. Neither of these target regions is consistently more similar to
380 the mouse caudoputamen over all latent spaces.

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

383 mouse targets is lower ($\sigma = 0.04$) compared with the equivalent variances for the caudate ($\sigma = 0.08$) and
384 putamen ($\sigma = 0.08$), indicating less specificity to any one mouse striatal target. In particular, the human
385 nucleus accumbens isn't as specifically similar to the mouse nucleus accumbens in the way that the caudate
386 and putamen are similar to the caudoputamen. The mouse target distributions are right-shifted compared
387 with those for the caudate and putamen, with median values of 0.89, 0.86, and 0.87 for the mouse nucleus
388 accumbens, caudoputamen, and fundus of striatum, respectively. The human accumbens also exhibits a high
389 degree of similarity to the mouse olfactory tubercle, the distribution of which is also right-shifted compared
390 with the caudate and putamen.

391 Given the high correlation of the human caudate and putamen to the mouse caudoputamen, as well as the
392 finding reported by Balsters et al. about the similarity of the lateral caudoputamen to the putamen, we were
393 curious as to whether we could identify sub-regional patterns of similarity in the caudoputamen and other
394 striatal regions using these gene expression data. To probe this question, we first examined the average
395 latent space correlation between each voxel in the mouse striatum and every region in the human atlas. We
396 created brain maps for the human regions that exhibited the highest mean correlation values, averaged over
397 mouse striatal voxels: the caudate, the putamen, the nucleus accumbens, and the septal nuclei (Figure 6B).
398 We find that voxels in the caudoputamen exhibit a homogeneous pattern of similarity to both the caudate
399 and the putamen. On average, voxels in the caudoputamen have a correlation of 0.92 to the caudate and
400 0.91 to the putamen, with standard deviations of 0.05 and 0.06 respectively. The caudate and putamen are
401 associated with correlations of at least 0.90 in 79% and 73% of caudoputamen voxels. A number of voxels
402 are also highly similar to the human nucleus accumbens, with an average correlation value of 0.86 and 30%
403 of voxels returning a correlation of at least 0.90. The caudoputamen voxels most similar to the nucleus
404 accumbens lie in the ventral-rostral part of the region. Of course, voxels in the mouse nucleus accumbens are
405 also highly similar to the human nucleus accumbens, with an average of 0.89 and standard deviation of 0.06.
406 While the human nucleus accumbens is the most strongly correlated region, a number of voxels also exhibit
407 reasonably strong correlations to the substantia innominata and the amygdala. Indeed, 88% of voxels in the
408 accumbens are correlated at a value of 0.7 or higher to the amygdala, and 57% of voxels pass this threshold
409 for the substantia innominata.

410 We additionally examined the proportion of latent spaces in which each voxel in the mouse striatum was
411 maximally similar to the human target regions (Figure 6C). As expected, we find that voxels in the cau-
412 doputamen are most often maximally similar to the human caudate and putamen, with 77% of voxels in
413 the caudoputamen being maximally similar to the caudate or putamen in at least 95% of latent spaces, and
414 59% of voxels being maximally similar to one of those targets in all latent spaces. Interestingly, we observe

415 the emergence of a continuous bilateral pattern of specificity to the caudate and putamen, with voxels in the
416 rostral and lateral-caudal parts of the caudoputamen being maximally similar to the caudate in a high pro-
417 portion of latent spaces. In contrast, while voxels in the medial-rostral part of the caudoputamen are often
418 maximally similar to the caudate, they are also maximally similar to the putamen in some of latent spaces.
419 This map highlights subtle differences in the similarity between caudoputamen voxels and the caudate or
420 putamen. While this pattern distinguishes the two regions on the basis of which is the top match, individual
421 voxels have very similar correlation values to the targets (Figure 6B), with a mean difference in correlation
422 of only 0.01. Beyond the caudoputamen, we find that the accumbens and olfactory tubercle in the mouse
423 are consistently similar to the human nucleus accumbens, with 84% of mouse accumbens voxels and 75% of
424 olfactory tubercle voxels having the human accumbens as their top match in at least 80% of latent spaces.
425 For those voxels below this threshold, the human regions that are most often the top match are the amygdala
426 and the piriform cortex.

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

437 Discussion

438 We have demonstrated how spatial transcriptomic patterns of homologous genes can be used to make quan-
439 titative comparisons between the mouse and human brain. We showed that using homologous genes as a
440 common space allows one to easily identify coarse similarities in brain structures across species, but that
441 more fine-scaled parcellations, such as at the level of cortical areas, are more complex. Despite this limi-
442 tation, the approach still allows for a formal assessment of different patterns of between-species similarity
443 in primary compared to supramodal regions, identifications of distinct clusters of cortical territories across
444 species, and comparison of between-species similarities at the transcriptomic level to those observed using

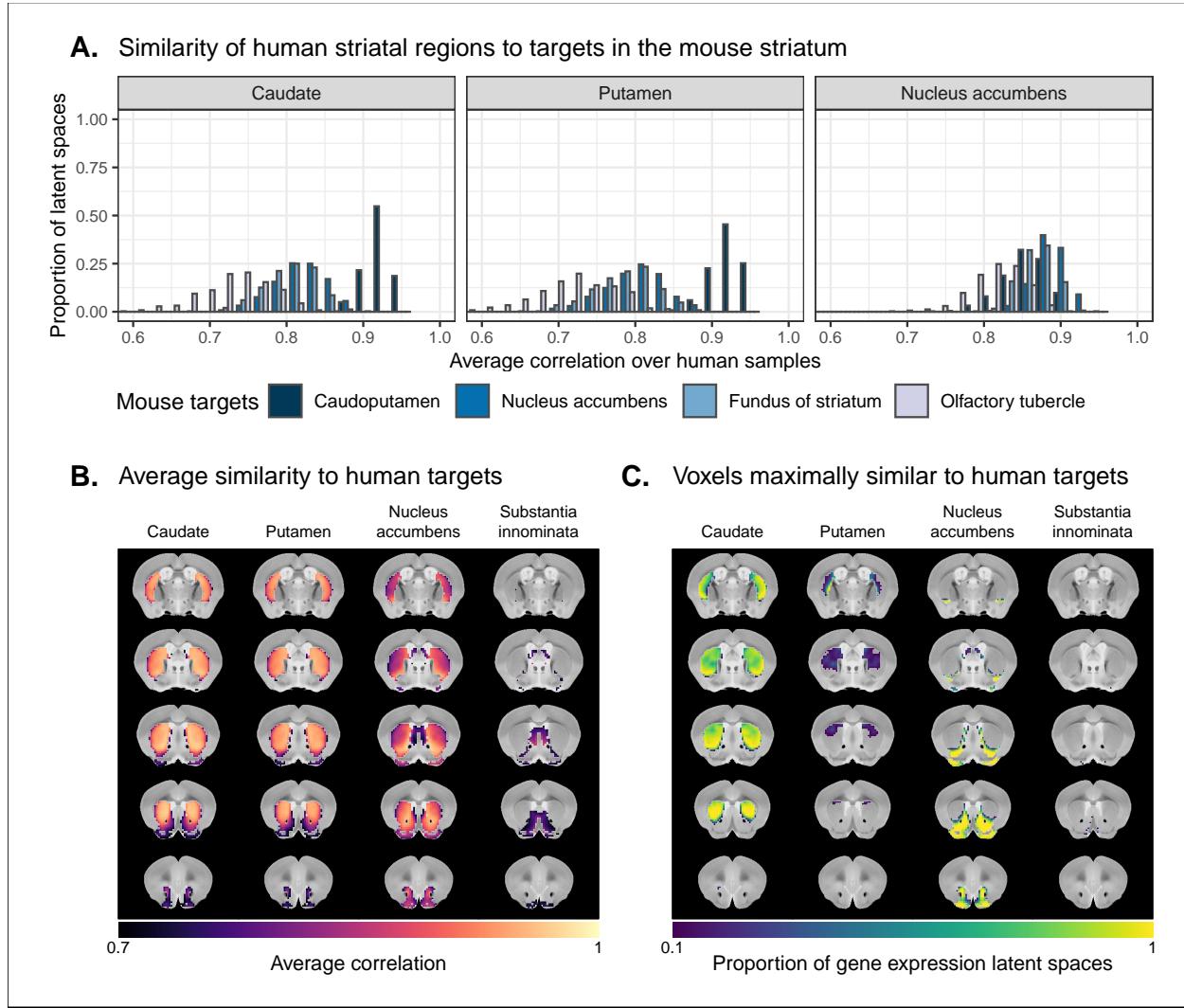


Figure 6. Similarity among mouse and human striatal regions. **(A)** Distributions over gene expression latent spaces of region-wise average correlation values for mouse and human striatal pairs. Human regions were chosen based on the AHBA ontology. Mouse target regions were chosen to be those with the 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.

445 other modalities. We will discuss our observations in the context of the importance of the mouse as a model
446 for human neuroscience below.

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

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

477 of homologous genes that can delineate areas within a single species.

478 This latent common space approach led to a substantial improvement in specificity of between-species com-
479 parisons. Nevertheless, it is evident that the first major distinction in gene expression patterns within a
480 species, and the easiest identification of similarity across species, is at the coarse anatomical level of the
481 major subdivisions of the vertebrate brain, such as the isocortex, cerebellar hemispheres and nuclei, and
482 brain stem. All of these territories were present in the ancestral vertebrate brain (Striedter and Northcutt,
483 2020) and the ability to detect conserved transcriptomic signatures at this level is not surprising. Within
484 such structures, such as the isocortex, our ability to make simple one-to-one correspondences decreased. This
485 is partly because areas within a coarse structure have more similar transcriptomic profiles, but also likely
486 due to the fact that a single area in one brain does not have a single correspondent in another, larger brain.
487 In other words, regions in the brains of related species may exhibit one-to-many or many-to-many mappings.
488 In our study, we found greater cross-species similarity between cortical areas associated with sensorimotor
489 processing than areas in supramodal cortex. Primary areas, including the sensorimotor areas, are present
490 in all mammals studied to date and likely part of the common ancestors of all mammals (Kaas, 2011a;
491 Krubitzer, 2007). Although this common ancestor likely also had non-primary areas, it cannot be denied
492 that association cortex expanded dramatically in primates and especially so in the human brain (Chaplin et
493 al., 2013; Mars et al., 2016a). Again, the pattern found here of greater similarity in more conserved areas
494 might reflect this evolutionary history. In that context it is interesting to note that some non-primary areas
495 thought to be present in the common mammalian ancestor, such as cingulate and orbitofrontal cortex (Kaas,
496 2011a) showed relatively high correlation to human areas.

497 An advantage of the approach presented here is that it can, in principle, be applied to any aspect of brain
498 organization. Beyond simply establishing whether areas are similar across species in a particular common
499 space, comparing the results across common spaces established using different types of neuronal data can
500 inform on which larger principles of organization are similar across brains (Eichert et al., 2020). This is
501 illustrated here by the results of our striatal analysis. We found high similarity between the human caudate
502 and putamen and mouse caudoputamen, with little differentiation within these regions in a single species.
503 In contrast, Balsters et al. (2020) demonstrated that human caudoputamen contains a distinct pattern of
504 connectivity. At first sight, one could argue the results are in contrast. However, evolutionarily speaking, it
505 is quite probable that an overall similar transcriptomic signature of the striatum can be accompanied by a
506 distinct connectivity pattern to areas of the cortex present in only one of the two species. Indeed, this speaks
507 to the different types of similarity that can be studied, depending on which aspect of brain organization one
508 is interested in. Although the human brain is much larger than the mouse brain and contains a number

509 of cortical territories that have no homologue in the mouse brain (Kaas, 2011b; Rudebeck and Izquierdo,
510 2022), the similarity in transcriptomic signature mean that translations between the species is valid in many
511 contexts.

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

525 Materials and methods

526 Mouse gene expression data

527 We used the adult mouse whole-brain in-situ hybridization data sets from the Allen Mouse Brain Atlas
528 (Lein et al., 2007). Specifically, we used 3D expression grid data, i.e. expression data aligned to the Allen
529 Mouse Brain Common Coordinate Framework (CCFv3)(Wang et al., 2020) and summarized under a grid
530 at a resolution of 200 μ m. We downloaded the gene expression “energy” volumes from both the coronal
531 and sagittal in-situ hybridization experiments as a sequence of 32-bit float values using the Allen Institute’s
532 API (<http://help.brain-map.org/display/api/Downloading+3-D+Expression+Grid+Data>). These volumes
533 were subsequently reshaped into 3D images in the MINC format. Origin, extents, and spacing were defined
534 such that the image was RAS-oriented, with the origin at the point where the anterior commissure crosses
535 the midline. The MINC images from the coronal and sagittal data sets were then processed separately
536 using the Python programming language. The sagittal data set was first filtered to keep only those genes
537 that were also present in the coronal set. Images were imported using the `pyminc` package, masked and

538 reshaped to form an experiment-by-voxel expression matrix. We pre-processed this data by first applying a
539 `log2` transformation for consistency with the human data set. For those genes associated with more than
540 one in-situ hybridization experiment, we averaged the expression of each voxel across the experiments. We
541 subsequently filtered out genes for which more than 20% of voxels contained missing values. Finally, we
542 applied a K-nearest neighbours algorithm to impute the remaining missing values. The result of this pre-
543 processing pipeline was a gene-by-voxel expression matrix with 3958 genes and 61315 voxels for the coronal
544 data set and a matrix with 3619 genes and 26317 voxels for the sagittal data set.

545 Human gene expression data

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

557 Mouse atlases

558 We used a version of the DSURQE atlas from the Mouse Imaging Centre (Dorr et al., 2008; Qiu et al., 2018;
559 Richards et al., 2011; Steadman et al., 2014; Ullmann et al., 2013), modified using the AMBA hierarchical
560 ontology, which was downloaded from the Allen Institute’s API. The labels of the DSURQE atlas correspond
561 to the leaf node regions in the AMBA ontology, which allowed us to use the hierarchical neuroanatomical
562 tree to aggregate and prune the atlas labels to the desired level of granularity. For the purposes of our
563 analyses, we removed white matter and ventricular regions entirely. The remaining grey matter regions were
564 aggregated up the hierarchy so that the majority of resulting labels contained enough voxels to be classified
565 appropriately by the multi-layer perceptron. In doing so, we maintained approximately the same level of
566 tree depth within a broad region (e.g. cerebellar regions were chosen at the same level of granularity). This

567 resulted in a mouse atlas with 67 grey matter regions. We additionally generated an atlas with 11 broader
568 regions for visualization and annotation purposes.

569 **Human atlases**

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

574 **Regional expression and similarity matrices**

575 We created the mouse and human gene-by-region expression matrices from the mouse gene-by-voxel and
576 human gene-by-sample expression matrices. First, we intersected the gene sets in these matrices with a
577 list of 3331 homologous genes obtained from the NCBI HomoloGene database (NCBI, 2018), resulting in
578 2835 homologous genes present in both the mouse and human expression matrices. We then annotated
579 each of the human samples with one of the 88 human atlas regions, and each of the mouse voxels with
580 one of the 67 mouse atlas regions, discarding white matter and ventricular entries in the process. These
581 labelled expression matrices were subsequently normalized as follows: For each matrix, we first standardized
582 every gene across all voxels/samples using a z-scoring procedure. We then centered every voxel/sample
583 by subtracting the average expression over all homologous genes. Finally, we generated the gene-by-region
584 expression matrices by averaging the expression of every gene over the voxels/samples corresponding to
585 each atlas region. Using these expression matrices, we generated the mouse-human similarity matrix by
586 computing the Pearson correlation coefficient between all pairs of mouse and human regions.

587 **Gene enrichment analysis**

588 We ran a gene enrichment analysis on the set of homologous genes obtained from the NCBI HomoloGene
589 database. We first downloaded Gene Ontology data for biological process related modules from the Bader
590 Lab at the University of Toronto (<http://baderlab.org/GeneSets>). These data include a gene set of 16563
591 genes and a module set of 15757 biological process modules. Every module is associated with a subset
592 of genes from the full gene set. For each module, we used a hypergeometric test to evaluate whether the
593 homologous gene set was over-represented in the module subset, compared with the full gene set. The

594 resulting p-values were adjusted for multiple comparisons using the false-discovery rate method (Benjamini
595 and Hochberg, 1995). A total of 938 modules were found to be significant at a threshold of 0.001. The
596 surviving modules were ordered according to their p-values and written out to a comma-separated values
597 data file (Supplementary File 1). This analysis was carried out using the `tmod` package in the R programming
598 language.

599 Multi-layer perceptron classification and latent space

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

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

634 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
635 using a maximum learning rate of 10^{-5} . We used the `AdamW` optimization algorithm (Loshchilov and Hutter,
636 2019) and `OneCycleLR` learning rate scheduler policy. The activation function used in the forward pass
637 was the rectified linear unit (ReLU) and the loss function was the negative log-likelihood loss, which is the
638 default for the `NeuralNetClassifier` class in `skorch`.

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

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

652 Multi-layer perceptron feature importance

653 We used integrated gradients to evaluate the contribution of different genes in the classification of mouse
654 atlas labels. Since the homologous gene inputs contribute to the classification of distinct labels in different

ways, we examined the feature attributions for three regions: the caudoputamen, the primary motor area, and the infralimbic area. Using the trained multi-layer perceptron, we computed integrated gradients for each of these three regions. We then averaged the values over all input voxels for each gene, resulting in a vector of gene attributions for each of the three example regions. This process was repeated for 200 training runs of the neural network. We then averaged the gene importance vectors of each region over all training runs to get a summary of gene importance. This process was implemented using the `IntegratedGradients` function from the `captum` package in Python (<https://captum.ai/>).

Quantifying improvement in gene expression latent spaces

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

Data and code availability

This manuscript and all figures were generated programmatically using R Markdown (<https://rmarkdown.rstudio.com>) and L^AT_EX(<https://www.latex-project.org>). The Allen Mouse Brain Atlas and Allen Human 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 and manuscript, is accessible at <https://github.com/abeaucha/MouseHumanTranscriptomicSimilarity/>.

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684 Competing interests

685 The authors declare that they have no competing interests.

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878 **Figure supplements**

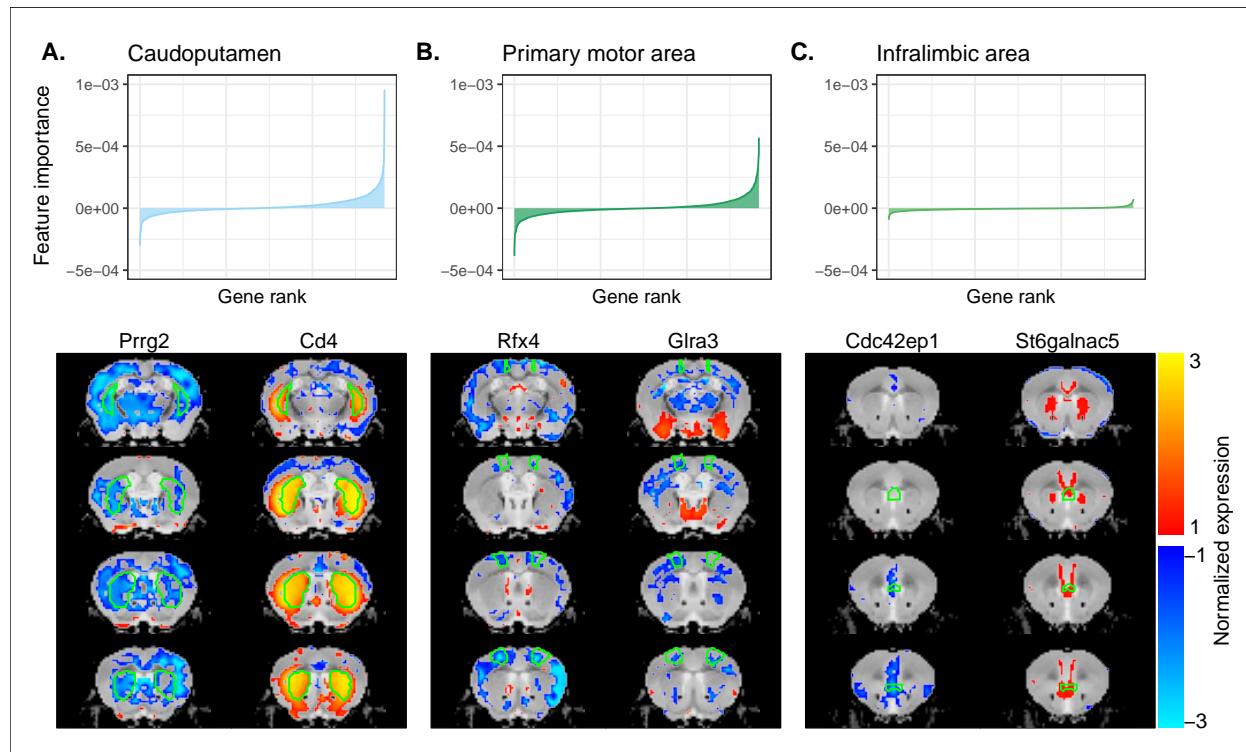


Figure 2-figure supplement 1. Multi-layer perceptron feature importance for the classification of the caudoputamen (**A**), the primary motor area (**B**), and the infralimbic area (**C**). Top row: Rank-ordered distributions of feature importance for the three example regions, averaged over 200 training runs. While the perceptron relies on information from all input genes, a reduced subset of genes is often more informative for the classification of a given label. Bottom row: Coronal slice series displaying the normalized expression patterns for the two genes most informative in the classification of example regions. The spatial expression patterns can be specific to the region of interest, but this is not necessarily the case.